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ELECTROCARDIOGRAPHIC STUDIES IN RHEUMATIC HEART DISEASE WITH REFERENCE TO INTERPRETATION OF MULTIPLE UNIPOLAR PRECORDIAL LEADS

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THE routine use of multiple unipolar precordial leads revealed the frequent occurrence of left ventricular hypertrophy, heart in the vertical position, and a clockwise rotation of the manifest mean electrical axis¹ (right axis deviation) in curves recorded from children with rheumatic heart disease. The idea that mitral stenosis is the leading factor in the production of right axis deviation, an electrocardiographic finding which is currently interpreted as evidence of right ventricular hypertrophy, is uniformly emphasized in texts on electrocardiography.²⁻⁵

METHOD AND MATERIAL

A comparison of relevant physical findings with telerepentgenograms and electrocardiograms was made. Study of the latter included a calculation of the mean electrical axis (A_{QRS}) and the electrical position of the heart and interpretation of multiple precordial leads V_1 , V_2 , V_3 , V_4 , V_5 , and V_6 . The precordial leads were recorded by utilizing the left arm terminal of the galvanometer for the exploring electrode and the right arm terminal for the reference electrode which was connected to a central terminal⁶ formed at the union of three wires, each connected to an extremity (the arms and the left leg).⁷ The positions explored were those specified by the Committee of the American Heart Association for the Standardization of Precordial Leads.⁸

In a comprehensive study⁹ of multiple precordial leads, it was found convenient to refer to the right or left side of the electrical precordium, according

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to whether the potential variations of the region specified are transmitted from the surface of the right or the surface of the left ventricle. When a lead yields potential variations which resemble those found both farther to the right and farther to the left, it is said to be of transition form, or to be recorded from the transition zone. The latter zone divides the right and left side of the electrical precordium and varies from position one through position six, according to the heart's position and to other factors. In this study we have followed this terminology in reference to "transition" and to the "right side" and "left side" of the "precordium."

Fifty patients with rheumatic fever were selected according to the following criteria:

1. A typical history of at least one attack of acute rheumatic fever.
2. Cardiac enlargement as evidenced by at least one of the following: physical signs, teleroentgenogram, or electrocardiographic examination.

RESULTS

Of the fifty selected patients, twenty-seven gave a history of repeated attacks of acute rheumatic fever for a period of several years. Twenty-three patients were examined during their initial attack, or shortly thereafter. The ages of the patients studied ranged from 4 to 29 years, with an average of 10 years. There were twenty-two male and twenty-eight female subjects. Cardiac enlargement was evidenced by physical signs in thirty-two, by teleroentgenogram in twenty-six, and by the electrocardiogram in forty-nine subjects. Of the latter group, right ventricular hypertrophy was evidenced in twenty-five and left ventricular hypertrophy in forty-one subjects. Both right and left ventricular hypertrophy occurred in nineteen subjects (Table I).

The electrical positions of the heart, classified according to Wilson and associates⁹ are itemized as follows:

POSITION	NUMBER OF CASES
Vertical	19
Semivertical	17
Intermediate	8
Semihorizontal	4
Horizontal	2
Indeterminate	0

The manifest mean electrical axis (A_{QRS}) showed clockwise rotation in twenty-one subjects, counterclockwise rotation in four, and normal axis in twenty-five. Eleven of the nineteen hearts which were classified as being in the vertical position yielded curves which showed evidence of right axis deviation in the limb leads and left ventricular hypertrophy in the precordial leads. The electrocardiograms of eight subjects indicated hypertrophy of both ventricles, heart in the vertical position, and clockwise rotation of A_{QRS} .

TABLE I. COMPARISON OF ELECTRICAL POSITION OF HEART, MANIFEST MEAN ELECTRICAL AXIS (A_{Qns}), AND SIZE OF HEART AS EVIDENCED BY ELECTROCARDIOGRAM, PHYSICAL SIGNS, AND TELEROENTGENOGRAM

ELECTRO-CARDIOGRAM	A_{Qns}	POSITION	PHYSICAL	TELEROENTGENOGRAM
L.V.P.	Right	Vertical	Marked enlargement	Slightly enlarged
L.V.P.	Right	Vertical	Normal	Normal
L.V.P.	Right	Vertical	Slight enlargement	Moderately enlarged
L.V.P.	Right	Vertical	Slight enlargement	---
L.V.P.	Right	Vertical	Moderate enlargement	Normal
L.V.P.	Right	Vertical	Marked enlargement	Moderately enlarged
L.V.P.	Right	Vertical	Marked enlargement	Markedly enlarged
L.V.P.	Right	Vertical	Moderate enlargement	Slightly enlarged
L.V.P.	Right	Vertical	Moderate enlargement	Moderately enlarged
L.V.P.	Right	Vertical	Moderate enlargement	Normal
L.V.P.	Right	Vertical	Marked enlargement	Markedly enlarged
L.V.P.	Right	Semivertical	Normal	---
L.V.P.	Right	Semivertical	Marked enlargement	Moderately enlarged
L.V.P.	Left	Horizontal	Marked enlargement	Moderately enlarged
L.V.P.	Left	Semihorizontal	Marked enlargement	Moderately enlarged
L.V.P.	Normal	Semivertical	Moderate enlargement	Normal
L.V.P.	Normal	Semivertical	Marked enlargement	Markedly enlarged
L.V.P.	Normal	Semivertical	Moderate enlargement	Normal
L.V.P.	Normal	Intermediate	Moderate enlargement	Moderately enlarged
L.V.P.	Normal	Intermediate	Normal	Normal
L.V.P.	Normal	Intermediate	Normal	Normal
L.V.P.	Normal	Intermediate	Normal	Normal
L.V.P.	Normal	Semihorizontal	Moderate enlargement	Moderately enlarged
R.V.P.	Normal	Semivertical	Normal	Normal
R.V.P.	Normal	Semivertical	Normal	Normal
R.V.P.	Normal	Semivertical	Normal	Normal
R.V.P.	Normal	Intermediate	Normal	Normal
R.V.P.	Normal	Intermediate	Normal	Normal
R.V.P.	Normal	Intermediate	Normal	Normal
Both	Right	Vertical	Normal	Slightly enlarged
Both	Right	Vertical	Slight enlargement	Normal
Both	Right	Vertical	Marked enlargement	Markedly enlarged
Both	Right	Vertical	Normal	Slightly enlarged
Both	Right	Vertical	Slight enlargement	Moderately enlarged
Both	Right	Vertical	Moderate enlargement	Moderately enlarged
Both	Right	Vertical	Slight enlargement	Slightly enlarged
Both	Right	Vertical	Normal	Normal
Both	Left	Semihorizontal	Moderate enlargement	Moderately enlarged
Both	Normal	Semivertical	Marked enlargement	Moderately enlarged
Both	Normal	Semivertical	Marked enlargement	Markedly enlarged
Both	Normal	Semivertical	Moderate enlargement	Moderately enlarged
Both	Normal	Semivertical	Marked enlargement	Moderately enlarged
Both	Normal	Semivertical	Normal	---
Both	Normal	Semivertical	Normal	Normal
Both	Normal	Semivertical	Moderate enlargement	Moderately enlarged
Both	Normal	Semivertical	Normal	Normal
Both	Normal	Intermediate	Normal	Normal
Both	Normal	Semihorizontal	Moderate enlargement	Normal
Normal	Normal	Semivertical	Marked enlargement	Moderately enlarged
R.B.B.B. (R.V.P.?)	Left	Horizontal	Moderate enlargement	Moderately enlarged

L.V.P., Left ventricular hypertrophy; R.V.P., right ventricular hypertrophy; Both, L.V.P. and R.V.P.; R.B.B.B., right bundle branch block; ---, not taken.

Of the curves indicating the semivertical position, there were two with clockwise rotation of A_{QRS} and evidence of left ventricular hypertrophy in the precordial leads. Fourteen curves showed normal A_{QRS} . Of these, eight showed evidence of hypertrophy of both ventricles, two showed left ventricular hypertrophy, three showed right ventricular hypertrophy, and one was a normal electrocardiogram.

Of the four curves which displayed counterclockwise rotation of A_{QRS} , two occurred in hearts having the semihorizontal position, of which one presented additional evidence of left ventricular hypertrophy, and the other, hypertrophy of both ventricles. Of the remaining two curves which displayed counterclockwise rotation of A_{QRS} and horizontal positions, one showed left ventricular hypertrophy, whereas the other showed incomplete right bundle branch block.

ELECTROCARDIOGRAMS ILLUSTRATING VENTRICULAR HYPERTROPHY IN THE VARIOUS ELECTRICAL POSITIONS

Fig. 1 shows the electrocardiogram recorded during an attack of rheumatic fever from a 15-year-old white boy four years after the initial attack. Mitral systolic and diastolic murmurs, along with evidence of moderate cardiac enlargement, were detected on physical examination, although the roentgenograms showed a normal cardiac silhouette. The electrocardiogram shows a prominent R at V_5 and V_6 which indicates left ventricular hypertrophy. The electrical position of the heart is vertical, and clockwise rotation of A_{QRS} is present.

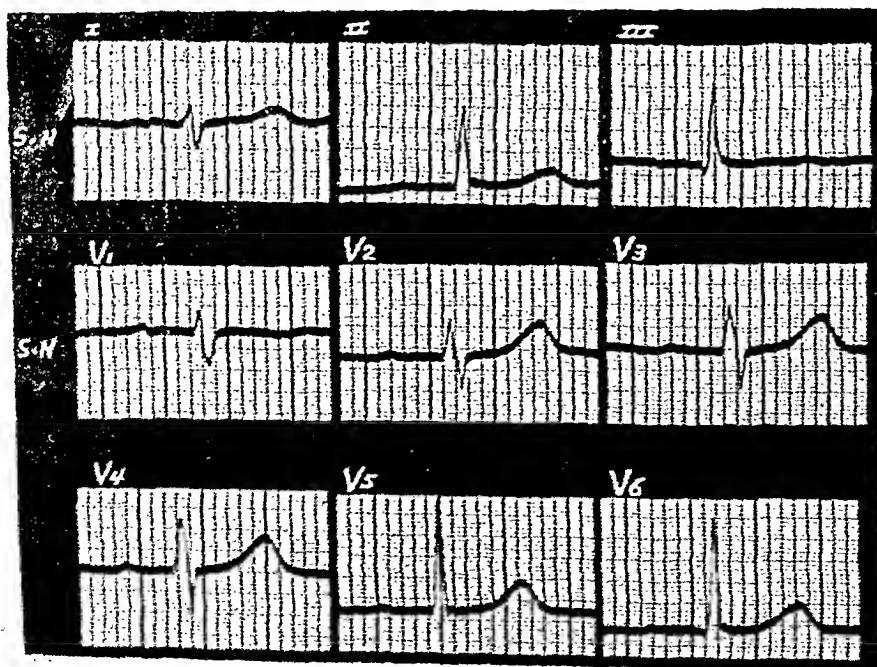


Fig. 1.—Child 15 years of age. Left ventricular hypertrophy; heart in the vertical position; clockwise rotation of A_{QRS} . V_1 and V_2 are from the right side of the precordium. Transition occurs at V_3 . V_4 , V_5 , and V_6 are from the left side of the precordium.

It should be noted that the limb leads might have been interpreted as right axis deviation resulting from right ventricular hypertrophy, and the popular method of taking only one precordial lead, V_4 , gives no added information inasmuch as the diagnostic deflection R is present only in V_5 and V_6 .

Fig. 2 is the electrocardiogram recorded from an 11-year-old white girl three months following the onset of an initial attack of acute rheumatic fever. Soft, blowing systolic and diastolic mitral murmurs were detected along with physical and roentgenographic evidence of moderate cardiac enlargement. In the electrocardiogram, R and S are prominent in Leads V_2 , V_3 , and V_4 from the right side of the precordium, and R is also prominent at V_5 and V_6 from the left side of the precordium, indicating both right and left ventricular hypertrophy. The electrical position of the heart is semivertical, and A_{QRS} is normal. There is also prolongation of the P-R interval with primary T-wave changes which may be taken as additional evidence of active rheumatic myocarditis.

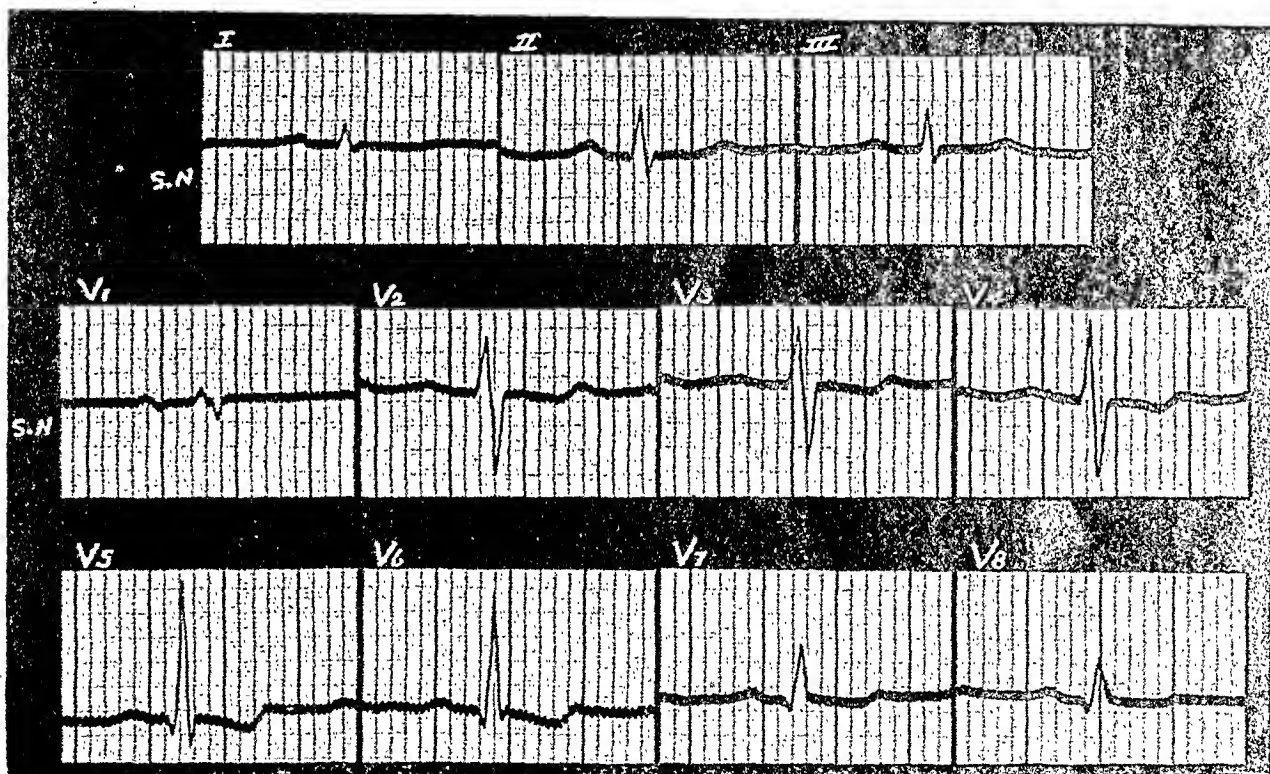


Fig. 2.—Child 11 years of age. Left and probably right ventricular hypertrophy; heart in the semi-vertical position; normal A_{QRS} . V_1 , V_2 , V_3 , and V_4 are from the right side of the precordium. Transition occurs between V_4 and V_5 . V_5 , V_6 , V_7 , and V_8 are from the left side of the precordium.

Fig. 3 is the electrocardiogram recorded from a 9-year-old white girl during an acute attack of rheumatic fever, three years following the initial attack. On physical examination, harsh mitral diastolic and soft, blowing mitral and aortic systolic murmurs were detected. The blood pressure was 125/62, and there was both physical and roentgenographic evidence of moderate cardiac enlargement. The electrocardiogram shows a prominent S at V_1 , V_2 , and V_3 . A prominent R occurs at V_5 and V_6 which are recorded at one-half normal stand-

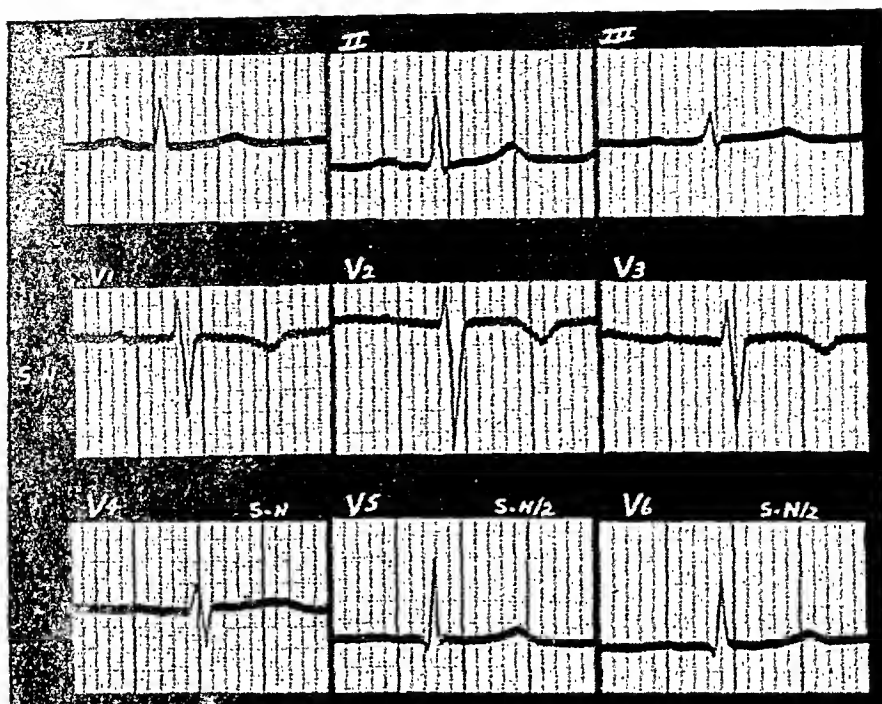


Fig. 3.—Child 9 years of age. Left ventricular hypertrophy; heart in the intermediate position; normal A_{QRS} . V_1 , V_2 , and V_3 are from the right side of the precordium. Transition occurs at V_4 . V_5 and V_6 , which are recorded at one-half normal standardization, are from the left side of the precordium.

ardization. These changes indicate left ventricular hypertrophy. The electrical position of the heart is intermediate, with normal A_{QRS} .

Fig. 4 is the electrocardiogram recorded from a 14-year-old white girl, who gave a history of repeated attacks of rheumatic fever accompanied by five years of cardiac decompensation. Physical examination revealed slight cardiac enlargement with a harsh presystolic mitral murmur extending through the first heart sound and accompanied by a palpable thrill. Teleroentgenograms were not made. The electrocardiogram shows a prominent S at V_2 and V_3 from the right side of the precordium, with a prominent R at V_5 and V_6 from the left side of the precordium, which indicate left ventricular hypertrophy. The electrical position of the heart is horizontal and counterclockwise rotation of A_{QRS} is present.

It is interesting to note that, in spite of mitral stenosis and congestive failure, left, rather than right, ventricular hypertrophy is present. Only one other patient in this series displayed a similar electrical position of the heart (Fig. 7).

ELECTROCARDIOGRAMS SUGGESTING TRANSIENT VENTRICULAR HYPERTROPHY

Figs. 5 and 6 show the electrocardiograms recorded from a 16-year-old white boy during the course of an initial attack of rheumatic fever. No murmurs were detected, and the heart did not appear to be enlarged on physical or roentgenographic examination. Fig. 5 shows a prominent S at V_2 and V_3 , which indicates left ventricular hypertrophy. The electrical position of the heart is vertical,

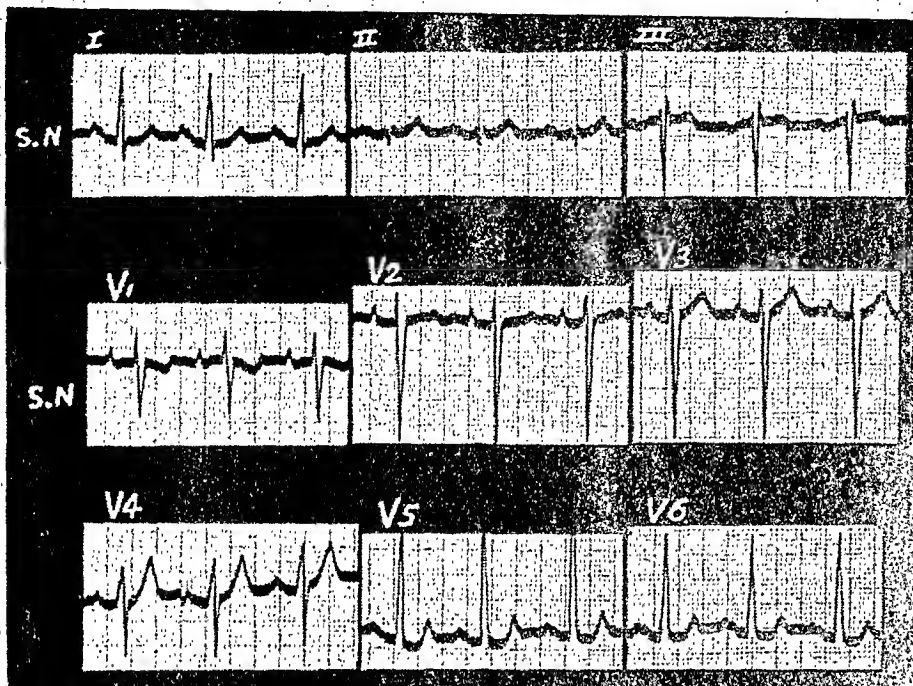


Fig. 4.—Child 14 years of age. Left ventricular hypertrophy; heart in the horizontal position; counterclockwise rotation of Aqrs. V₁, V₂, and V₃ are from the right side of the precordium. Transition occurs at V₄. V₅ and V₆ are from the left side of the precordium.

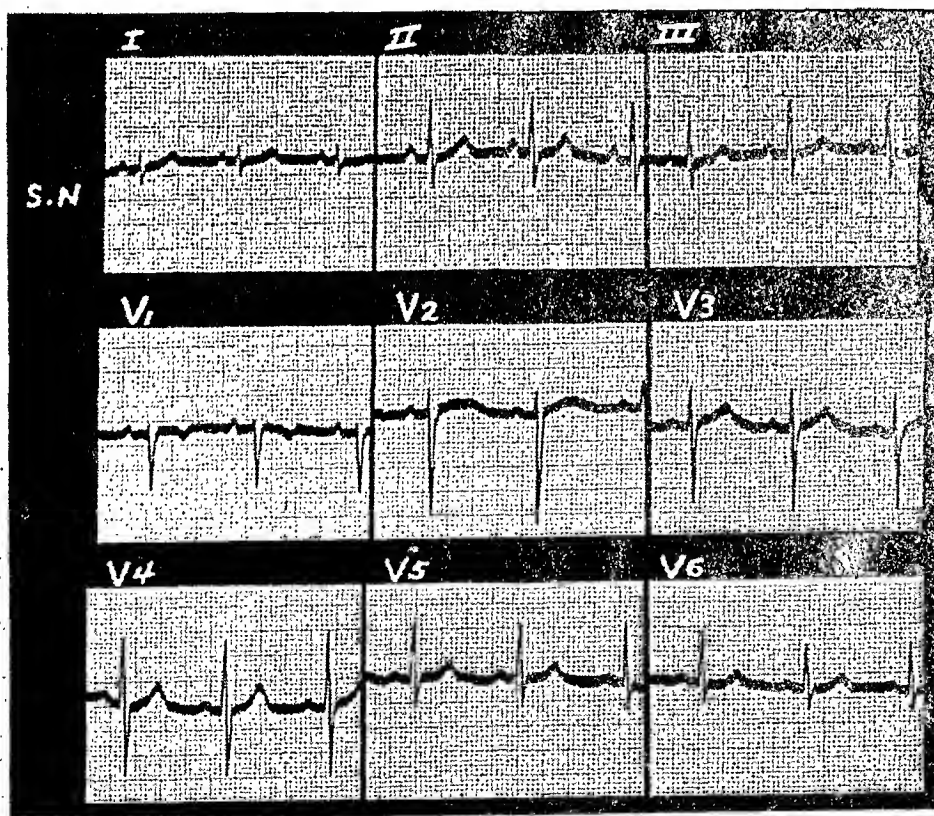


Fig. 5.—Adolescent boy 16 years of age. Left ventricular hypertrophy; heart in the vertical position; clockwise rotation of Aqrs. V₁, V₂, and V₃ are from the right side of the precordium. Transition occurs at V₄. V₅ and V₆ are from the left side of the precordium.

and there is a clockwise rotation of A_{QPS} . Fig. 6, recorded thirty days later, shows a normal electrocardiogram, in which the electrical position is semivertical and A_{QPS} is normal.

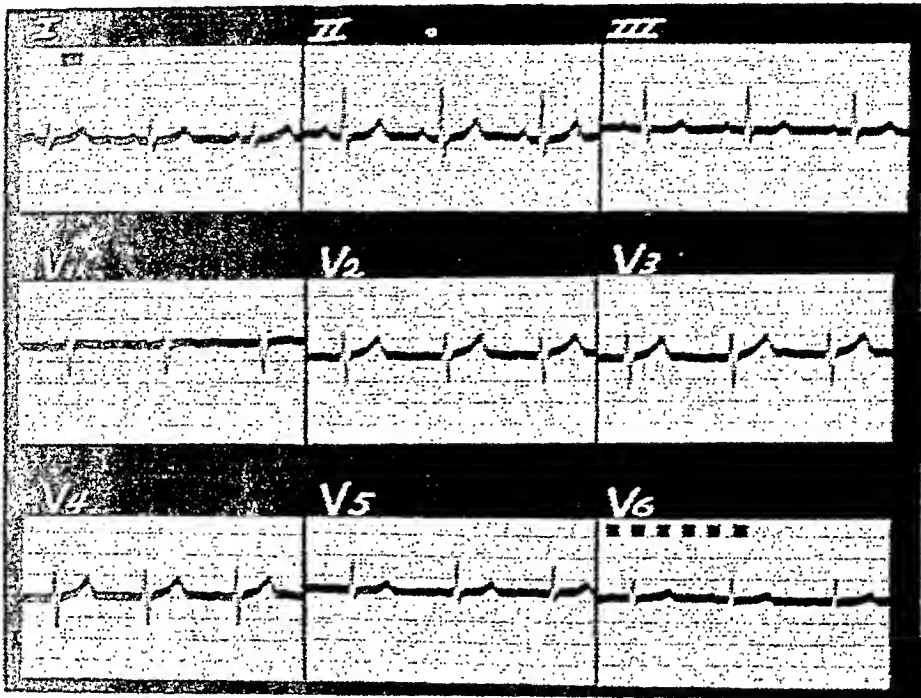


Fig. 6.—Normal electrocardiogram; heart in the semivertical position; normal A_{QPS} . Curve recorded thirty days following that shown in Fig. 5.

Three subjects were observed in whom electrocardiographic evidence of "ventricular hypertrophy" was present during the acute stage of rheumatic fever, while in subsequent curves, recorded after subsidence of the acute symptoms, the tracings were normal.

ELECTROCARDIOGRAMS OF UNUSUAL FORM

Fig. 7 is the electrocardiogram recorded from a 6-year-old white girl following five years of repeated attacks of rheumatic fever. Examination revealed harsh diastolic mitral and harsh systolic pulmonary and mitral murmurs, with both physical and roentgenographic evidence of moderate cardiac enlargement. The electrocardiogram shows a broad S in Lead I.¹⁹ All standard precordial leads, including V_7 and V_6 , present an initial R followed by a broad S, and the chief downstroke is early in the QRS interval. Unipolar leads recorded from the right hemithorax show that the downstroke of R occurs at the end of the QRS interval (see V_5' , V_6' , and V_7'). Two R deflections are present at V_E and V_F . These findings are diagnostic of incomplete right bundle branch block. The heart is in the horizontal position and counterclockwise rotation of A_{QPS} is present.

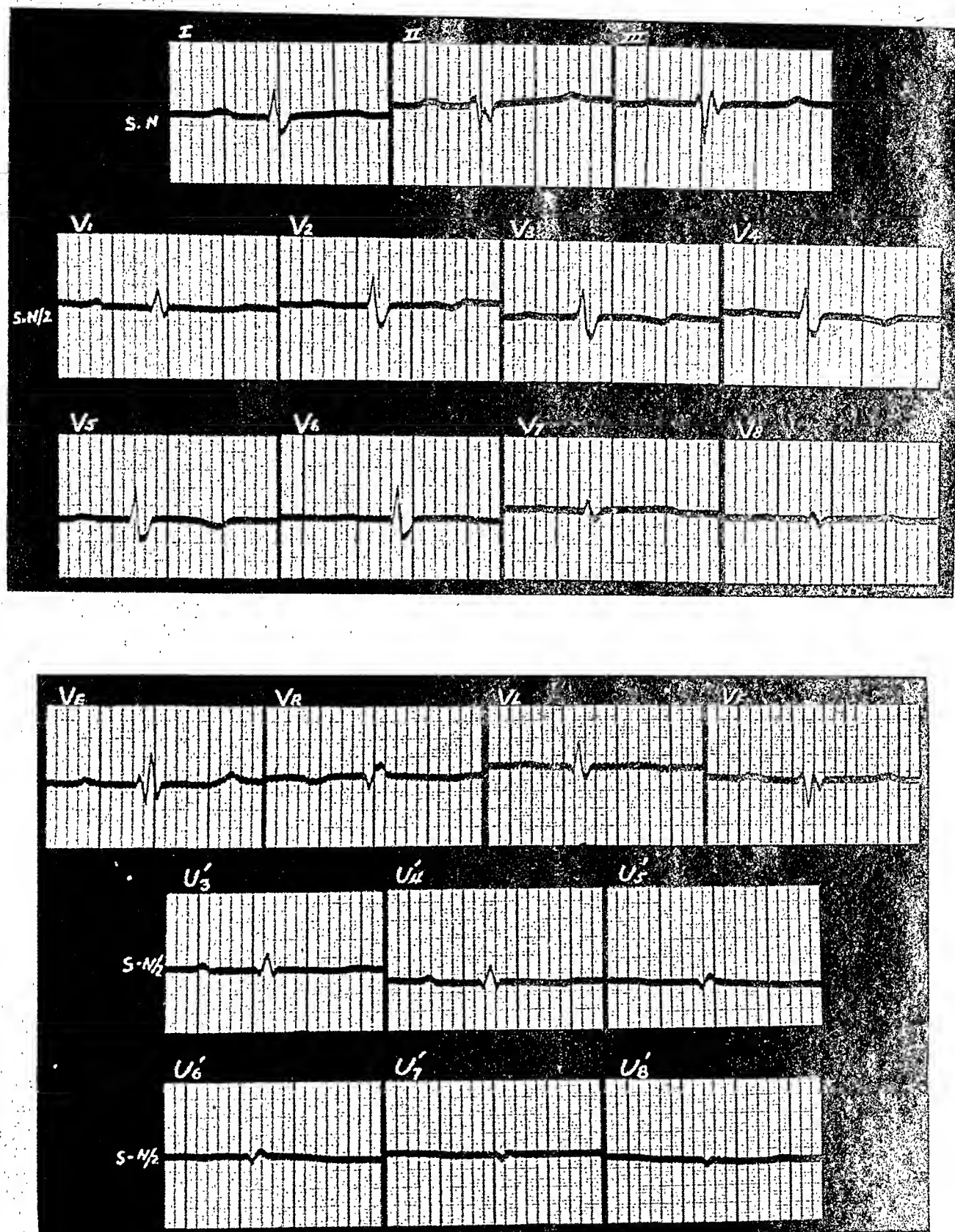


Fig. 7.—Child 6 years of age. Incomplete right bundle branch block; heart in the horizontal position; counterclockwise rotation of AQRS. Precordial leads V₁ through V₈ are from the left side of the precordium. V_E is the unipolar lead from the midepigastric region. V_R, V_L, and V_F are unipolar leads from the extremities indicated by subscript. V'₃, V'₄, V'₅, V'₆, V'₇, and V'₈ are unipolar leads recorded from the right hemithorax at positions symmetrical with the standard precordial leads of corresponding subscript. All chest leads are recorded at one-half normal standardization.

It is interesting to note that all of the standard precordial leads recorded from this subject are from that part of the precordium to which the free wall of the left ventricle transmits its potential variations. The free wall of the right ventricle is on the diaphragm and transmits its potential variations to the lateral and posterior portion of the right hemithorax, to the epigastrium, and to the left leg.

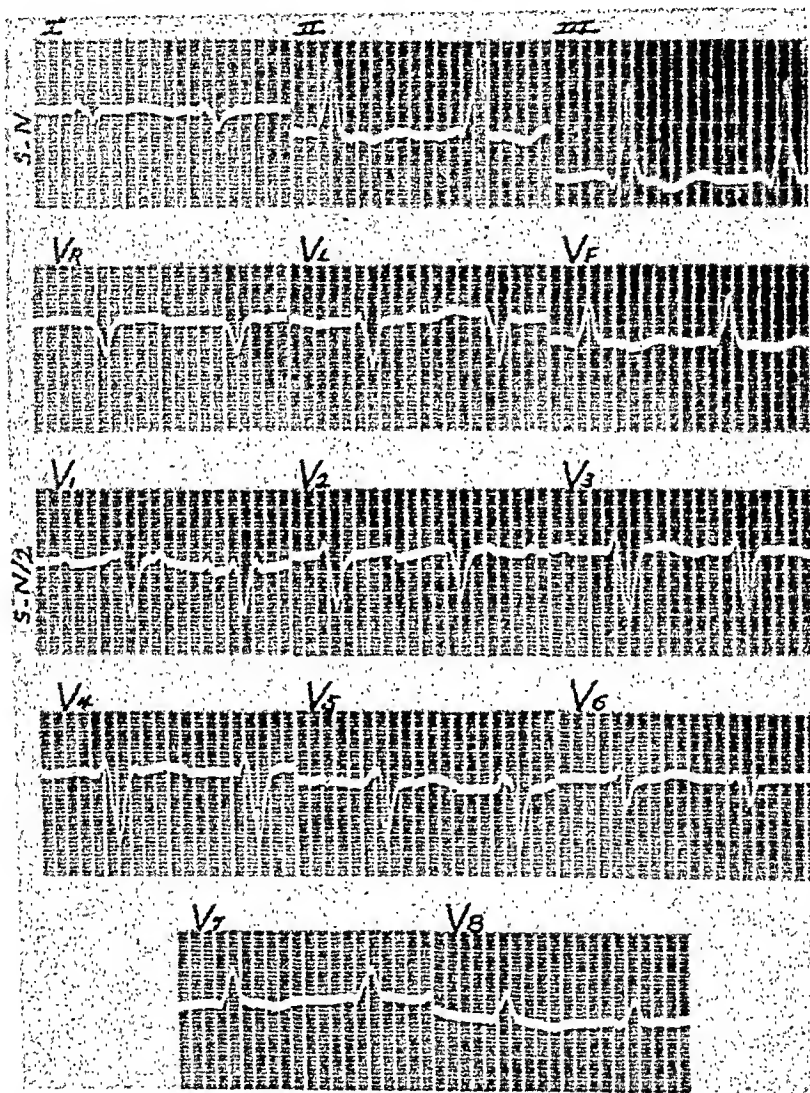


Fig. 8.—Child 12 years of age. Left ventricular hypertrophy; heart in the vertical position; clockwise rotation of Aqrs. Auricular fibrillation with rapid ventricular rate. Precordial leads V_1 through V_6 are from the right side of the precordium. Transition occurs between V_6 and V_7 . V_7 and V_8 are from the left side of the precordium. Chest leads recorded at one-half normal standardization.

Fig. 8 is the electrocardiogram recorded from a 12-year-old white boy 7 years of age following an initial attack of rheumatic fever and three years following the onset of auricular fibrillation and myocardial decompensation. Examination revealed harsh mitral systolic and diastolic murmurs which completely obliterated

ated the first heart sound, and both physical and roentgenographic evidence of marked cardiac enlargement were present. The electrocardiogram shows a small R and prominent S in precordial leads V_1 through V_6 from the right side of the precordium, with a prominent R at V_7 and V_8 from the left side of the precordium. Unipolar extremity leads show deflections at the left shoulder (V_L) which resemble those from the right side of the precordium and deflections at the left leg (V_F) which resemble those of the left side of the precordium. These changes are diagnostic of left ventricular hypertrophy, heart in the vertical position, and clockwise rotation of A_{QRS} . Auricular fibrillation with rapid ventricular rate is also present.

It is of interest to note that all standard precordial leads, V_1 through V_6 , recorded from this subject display potential variations which are transmitted from the right ventricle; the transition zone occurs between V_6 and V_7 ; V_7 and V_8 show potential variations transmitted from the left ventricular surface. Left ventricular hypertrophy is present, notwithstanding the fact that the patient has presented a clinical picture of mitral stenosis for several years.

A comparison of these findings with those of Fig. 7 reveals that the potential variations of the surface of either the left or of the right ventricle may be transmitted to that region of the precordium examined by Leads V_1 through V_6 , depending upon the electrical position of the heart.

DISCUSSION

It would appear that left ventricular hypertrophy occurs more frequently as a result of rheumatic heart disease than does right ventricular hypertrophy. This, we feel, is based on the tendency of rheumatic myocarditis to involve predominantly the walls of the left ventricle.

As pointed out by Wilson and co-workers,⁹ left ventricular hypertrophy in an electrically vertical heart produces clockwise rotation of the manifest mean electrical axis (A_{QRS}). Since the vertical and semivertical electrical positions are the most common in the age group of patients studied, it follows that a large number should show right axis deviation in the limb leads with evidence of left ventricular hypertrophy in the precordial leads.

Our observations confirm those of Taussig and Goldenberg¹¹ in that cardiac enlargement was not directly related to the endocardial (valvular) lesions and in that valvular lesions were not the prime factor in producing ventricular hypertrophy. In this connection, the electrocardiogram in Fig. 4 is one of many instances in which there is definite evidence of left ventricular hypertrophy, notwithstanding the fact that mitral stenosis was present. Many subjects studied (not included here) had clinical evidence of acute or chronic rheumatic heart disease unaccompanied by cardiac enlargement.

Thus far, we have used the term hypertrophy when the R and S deflections in the precordial leads exceeded the standard offered by Wilson and associates.⁹⁻¹² It should be pointed out, however, that cardiac dilatation, which produces a closer proximity of the ventricular and the thoracic walls, may, by

diminishing the distance from the exploring electrode to the accession wave, produce QRS deflections similar to those of hypertrophy. In subjects with electrocardiographic evidence of an initial increase in ventricular size and later a return to normal (Figs. 5 and 6), dilatation, rather than hypertrophy, probably predominates.

In Fig. 5, the T deflection at V_2 is low and notched, whereas a subsequent curve, Fig. 6, shows normal T deflections at all precordial leads. On frequent occasions the curves from subjects with acute rheumatic fever have shown abnormalities of RS-T and T in one or more of Leads V_1 , V_2 , and V_3 . The current method of recording the limb leads and only one precordial lead will rarely reveal these changes.

Curves similar to that shown in Fig. 7, which almost certainly indicate incomplete right bundle branch block, may occasionally be confused with ventricular hypertrophy. A consideration of the standard six precordial leads, which show an R followed by a prominent S at all positions, might indicate right ventricular hypertrophy, incomplete right bundle branch block, or both if the heart is in the horizontal position, or, might indicate left ventricular hypertrophy, incomplete left bundle branch block, or both if the heart is in the vertical position. Furthermore, V_7 and V_8 do not settle the disputation. On the other hand, further examination of the limb leads with the view of estimating the form of V_F^* leads directly to the proper diagnosis of incomplete right bundle branch block with the heart in the horizontal position. Added unipolar leads were utilized in order to confirm the diagnosis. Right ventricular hypertrophy cannot be excluded. A similar problem arises in connection with the diagnosis of hypertrophy from the electrocardiogram of Fig. 8.

SUMMARY

1. In the majority of subjects having rheumatic heart disease, left, rather than right, ventricular hypertrophy is responsible for clockwise or counter-clockwise rotation of the manifest mean electrical axis (A_{QRS}) according to whether the electrical position of the heart is vertical or horizontal.

2. Typical electrocardiograms are presented illustrating "ventricular hypertrophy" in the various heart positions with associated diversions of A_{QRS} .

3. Myocardial, rather than endocardial (valvular), lesions play the primary role in producing ventricular enlargement.

4. Abnormalities of the final ventricular deflections in the first three precordial leads are of added value in the diagnosis of acute rheumatic fever.

5. Curves are presented which illustrate that standard positions V_1 through V_6 may, in certain instances, represent the potential variations from the surface of one ventricle, either the right or left, depending upon the position of the heart. In one such curve the proper interpretation of incomplete right bundle branch block was made only after a reconsideration of the limb leads, together with Leads V_1 through V_6 .

* $V_F = \frac{LII + LIII}{2}$

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THE DURATION OF THE ELECTRICAL SYSTOLE (Q-T) IN ACUTE RHEUMATIC CARDITIS IN CHILDREN

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THE clinical and pathologic relationship of carditis and rheumatic fever was demonstrated conclusively by Bouillard over one hundred years ago.¹ The prognosis in rheumatic disease, however, was based almost entirely upon the state of the valves until about fifty years ago, when the function of the heart muscle came to be studied in detail. And as late as 1924, Cohn and Swift² stated that it was not possible to say during the course of the acute stage of rheumatic fever, "whether heart disease is likely to be established." They were of the opinion that long periods of time were often required to pass after the acute episode before the diagnosis of heart disease became apparent.

In recent years the scene of interest has changed from the study of valvular damage to that of acute rheumatic carditis. It has become apparent to students of rheumatic fever in children that carditis is the most frequent manifestation of rheumatic fever and is most often insidious and subclinical.³ From the diagnostic, prognostic, and therapeutic standpoints, acute rheumatic carditis is now recognized by most clinicians as being the most important manifestation of rheumatic fever.

But despite the great increase in the knowledge of the natural history of rheumatic disease and its cardiac manifestations, no clear-cut diagnostic criteria have been forthcoming. No criteria have been established for arriving at a judgment as to when rheumatic carditis is present, even in the case of obvious affection of the cardiac valves. The laboratory aids in diagnosis of rheumatic fever currently used have been disappointing in determining when the rheumatic inflammatory process in the heart muscle has begun or has ceased.⁴

In recent years, this field has been extensively yet inconclusively explored with the aid of the electrocardiograph. Considerable difference of opinion, however, exists with regard to the frequency of electrocardiographic abnormalities in patients suffering from acute rheumatic disease. The percentage incidence of electrocardiographic abnormalities ranges from 22 to 100 per cent in various studies. Of the fourteen most extensive reports up to 1941, one-half agree that abnormalities significant of involvement of the heart are found in 90 per cent or more of patients with rheumatic disease when frequent cardiac-

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graphic tracings are taken.⁵ The most frequent abnormal finding is a prolongation of the auriculoventricular (P-R) conduction time.

The addition of precordial leads has increased the incidence of abnormal electrocardiographic findings in rheumatic fever. Lead IV was found of clinical value as an aid in the recognition of myocardial involvement in rheumatic fever; successive changes were interpreted as showing that the cardiac lesions were not in a quiescent state.⁶ Convincing evidence has been reported showing that abnormal precordial leads are found with greater frequency than abnormal limb leads in children with active rheumatic disease.⁷

A critical review of the literature on electrocardiography in rheumatic fever emphasizes the fact that the electrocardiogram cannot be used as a specific diagnostic test for rheumatic carditis. The evidence presented is, in the main, of three sorts: (1) the duration of the A-V conduction time is increased, though not always; (2) there is frequent alteration in the ventricular complex, either the QRS, the S-T segment, or the T wave; (3) occurrence of irregularities in cardiac rhythm. It is pointed out that most electrocardiographic findings are transient and bear no clear-cut relationship to the clinical findings. Some alterations become fixed and cannot, therefore, be used as criteria for active carditis. Most electrocardiographic abnormalities described demonstrate evidence of temporary ischemia or permanent scar formation of the cardiac muscle. These findings seem to point to an inadvertent attempt to correlate electrocardiographic findings with the histopathology known to exist in rheumatic myocarditis. Few studies take into clear account the pathologic physiology mirrored in the cardiogram in the acutely inflamed heart muscle.

Physiologists have always contended that disturbance in time relationship of systole and diastole is a manifestation of impairment of the functional integrity of the myocardium. Wiggers and Clough⁸ found consistently that the period of systole was of longer duration in functional cardiac disorders. They made the observation that when more blood returns to the ventricle, it responds by expelling more blood not only by a greater number of ejection periods, but also by a greater relative duration of each systole. Katz⁹ has stated that the duration of systole in the diseased heart as compared with the normal heart would give a method of determining the functional integrity of the myocardium. Bazette¹⁰ concluded from his evidence that the duration of systole in the abnormal heart may prove a measure of dilatation.

There is a wide difference of opinion, however, among physiologists and clinicians regarding the clinical importance of the measurement of the duration of the electrical systole (Q-T). Katz¹¹ has stated that "there is little practical value in measuring the duration of electrical systole." Ashman and Hull¹² on the other hand, believe that the measurement of the electrical systole may give valuable information regarding the degree to which the myocardium is being affected in diphtheria or in acute rheumatic carditis. Cheer¹³ presented evidence to show that the electrical systole is greatly increased in heart failure irrespective of etiology and proposed the concept that an increased electrical systole may indicate a disturbance in cardiodynamics which might well be formed before clinical

evidence of failure is available. Tung¹⁴ showed that the measurement of electrical systole may be used in the differentiation of pericardial effusion with heart failure from acute dilatation with failure; the Q-T interval is prolonged in the latter instance. Drawe and associates¹⁵ found that the Q-T interval is definitely prolonged in about 25 per cent of the children with rheumatic disease whom they observed.

On the other hand, White and Mudd¹⁶ concluded from an extensive study that the duration of the Q-T interval is apparently of little or no clinical value. They found no prolongation in patients with structural cardiac defects. In functional cardiac disturbances they found a prolonged Q-T interval only in paroxysmal tachycardias or disorders causing a marked widening of the QRS complex. Dock¹⁷ stated that the duration of the Q-T interval is not a satisfactory index of cardiac function since only one-third of patients with failing hearts have systoles longer than the maximum found in normal subjects of the same sex and since the duration of the Q-T interval is the same in hypertensive patients with left ventricular preponderance without failure as in those who are badly decompensated.

It is clear, therefore, that while physiologists are in agreement that the prolongation of the duration of systole is significant of a disturbance in the functional integrity of the myocardium, clinically, insufficient evidence has been brought forth to support this physiologic concept. This discordance of opinion may be explained in part by the fact that the study of the component parts of the cardiac cycle have not been closely investigated in hearts showing an acute impairment of myocardial function but rather in cardiac conditions of long standing in which functional compensation has already been established at a given level of cardiac reserve. The study of children suffering from acute rheumatic carditis offers the opportunity to investigate the sequence of events in the cardiac cycle in a heart whose integrity is being actively impaired. On physiologic grounds, the duration of systole, both absolute and relative to diastole, in such hearts should be significantly disturbed. With this in mind, the following study was made.

PATIENTS STUDIED

A group of one hundred boys and girls from 7 to 14 years of age were studied under controlled conditions at the St. Francis Sanatorium for Cardiac Children. Fifty of these were observed during an episode of acute carditis* and for many months following rheumatic activity. The majority of the "active" group of cases were observed from the onset of carditis. A few were studied during a severe fulminating bout of pancarditis following a period of mild rheumatic activity. The other fifty boys and girls were observed during many months of quiescent rheumatic disease. The rheumatic disease in the majority of these had been quiescent for a minimum of twelve months prior to the period of observation;

*Only those children who presented both clinical and laboratory evidence of rheumatic carditis were included in this group.

in none, for less than six months. No intercurrent infections were observed during the study period in this group of children.

The age distribution in both "active" and "inactive" groups was practically the same. No significant difference in the extent of valvular involvement and the incidence and degree of cardiac enlargement was noted in the two groups. Children having auricular fibrillation or paroxysms of auricular or ventricular tachycardia were not included in this study. Those having marked intra-ventricular conduction disturbances were excluded from this investigation.

During the time that this study was in progress, none of the children received digitalis, salicylates, mercurials, or any form of intravenous therapy. Those who had received digitalis less than thirty days prior to the period of observation are not included in this study. All "inactive" children were ambulatory and participated in normal childhood activities. The "active" group were at complete bed rest during the entire period of rheumatic activity.

METHOD OF STUDY

Frequent electrocardiograms were made. These included the standard limb leads and three precordial leads (CF_2 , CF_4 , and CF_6). All electrocardiograms were taken with the patient in the recumbent position. The ambulatory patients were given a short rest period before tracings were taken. Clinical examination of the patient and pertinent laboratory tests were done at about the same time as the electrocardiograms were taken.

The Q-T and T-Q intervals were measured with the aid of a magnifying glass. Measurements were done in all leads and recorded. A minimum of twelve successive cycles were measured and the mean calculated. The duration of the Q-T was corrected for rate according to Bazette's formula.* The cardiac cycles used in the calculations were those used in measuring the actual Q-T interval.

All evaluations of the degree of rheumatic carditis in the "active" group were made without knowledge of the electrocardiographic measurements at the time of assessment. Likewise, the observation of the "inactive" group of children for rheumatic activity was done without the aid of the electrocardiograms.

RESULTS

Duration of Electrical Systole (Q-T).—Table I shows that the actual and corrected Q-T intervals are significantly longer in patients with acute carditis than in those with quiescent rheumatic disease. The average Q-Tc† for the "active" cases was 0.4374 second, as compared with 0.3924 second for the quies-

*The duration of the Q-T interval varies greatly with the length of the cardiac cycle. Consequently, in order to know whether a given Q-T is of normal length or not, one must know the normal length for the particular rate. This is expressed by Bazette's formula:

$$Q-T \text{ corrected} = \frac{Q-T \text{ interval in seconds}}{\sqrt{\text{Cardiac cycle in seconds}}}$$

†The corrected Q-T will be referred to here as Q-Tc.

TABLE I. DURATION OF ELECTRICAL SYSTOLE, BOTH ABSOLUTE AND RELATIVE TO DIASTOLE, IN FIFTY PATIENTS WITH ACUTE RHEUMATIC CARDITIS AND IN FIFTY PATIENTS WITH QUIESCENT RHEUMATIC FEVER

ACUTE CASES				QUIESCENT CASES			
RATE	Q-T	Q-Tc*	$\frac{Q-T}{T-Q}$	RATE	Q-T	Q-Tc	$\frac{Q-T}{T-Q}$
80	0.4036	0.466	1.13	72	0.3640	0.397	0.78
84	0.3800	0.449	1.16	72	0.3584	0.392	0.76
86	0.3760	0.445	1.19	72	0.3440	0.376	0.70
86	0.3580	0.423	1.05	74	0.3280	0.372	0.72
86	0.3864	0.457	1.22	76	0.3448	0.390	0.77
87	0.3660	0.436	1.14	76	0.3610	0.402	0.83
87	0.3720	0.447	1.16	77	0.3400	0.386	0.77
89	0.3520	0.428	1.08	77	0.3448	0.387	0.79
93	0.3480	0.435	1.17	79	0.3408	0.391	0.80
94	0.3484	0.435	1.20	79	0.3384	0.389	0.80
95	0.3620	0.455	1.32	79	0.3416	0.391	0.82
97	0.3424	0.434	1.26	80	0.3420	0.395	0.88
97	0.3340	0.425	1.15	81	0.3376	0.392	0.84
98	0.3292	0.423	1.14	81	0.3448	0.399	0.88
98	0.3484	0.445	1.14	81	0.3412	0.396	0.87
101	0.3392	0.438	1.34	82	0.3388	0.391	0.87
102	0.3428	0.444	1.41	82	0.3332	0.389	0.82
102	0.3280	0.426	1.17	83	0.3200	0.376	0.80
105	0.3400	0.444	1.46	83	0.3324	0.391	0.90
105	0.3200	0.421	1.22	83	0.3460	0.405	0.91
107	0.3400	0.450	1.54	85	0.3352	0.398	0.95
107	0.3244	0.433	1.38	85	0.3264	0.387	0.85
108	0.3472	0.466	1.67	86	0.3264	0.389	0.97
108	0.3192	0.428	1.34	86	0.3380	0.402	0.93
111	0.3150	0.428	1.36	87	0.3240	0.391	1.00
111	0.3200	0.436	1.45	87	0.3400	0.408	0.96
111	0.3192	0.435	1.45	87	0.3264	0.392	0.89
113	0.3212	0.443	1.57	87	0.3312	0.398	0.91
113	0.3144	0.432	1.31	88	0.3200	0.387	0.80
113	0.3412	0.466	1.80	88	0.3240	0.393	0.90
115	0.3028	0.420	1.38	89	0.3200	0.390	0.91
116	0.3200	0.446	1.63	90	0.3250	0.405	0.95
118	0.3212	0.451	1.72	90	0.3180	0.390	0.92
118	0.3100	0.436	1.64	92	0.3360	0.400	1.05
119	0.2984	0.419	1.45	93	0.3032	0.379	0.92
120	0.2920	0.413	1.39	95	0.3064	0.385	0.92
122	0.2920	0.415	1.45	95	0.3132	0.394	0.97
123	0.2920	0.418	1.49	96	0.2948	0.375	0.93
124	0.3200	0.455	1.95	101	0.3164	0.405	1.13
125	0.3024	0.436	1.69	101	0.3064	0.394	1.06
126	0.2960	0.427	1.64	102	0.3024	0.390	1.02
128	0.2912	0.425	1.63	102	0.3052	0.394	1.08
129	0.3000	0.438	1.82	102	0.3036	0.391	1.07
129	0.2924	0.429	1.62	103	0.3084	0.400	1.13
129	0.3016	0.441	1.86	103	0.3068	0.398	1.12
133	0.2920	0.437	1.91	105	0.3100	0.403	1.19
134	0.3144	0.471	1.99	105	0.2724	0.361	0.92
136	0.2864	0.430	1.55	107	0.3004	0.401	1.14
150	0.2800	0.443	2.33	113	0.2840	0.390	1.17
154	0.2628	0.430	2.04	117	0.2912	0.405	1.32
Av. 114	0.3261	0.4374	1.463	88.7	0.3276	0.3924	0.9278

*Q-Tc refers to the corrected Q-T interval.

cent cases. Since the average duration of the Q-T interval in normal children is said to be 0.325 second¹⁸ and the upper limit of the normal Q-Tc for children is 0.405 second,¹² it is apparent from our observation that the duration of systole of practically all children with quiescent rheumatic disease is within normal limits. On the other hand, all those with acute carditis have a systole significantly longer than the upper limit of normal. The shortest Q-Tc in this group was found to be moderately longer than the longest Q-Tc for the quiescent group.

Relation of Electrical Systole to Cardiac Rate.—It is well known that systole shortens appreciably with increasing cardiac rate. It is also widely appreciated that the cardiac rate in acute carditis is higher than in quiescent hearts. It is thus of great significance to find that the duration of systole is markedly longer in acute carditis than in the quiescent heart irrespective of cardiac rate. It will be noted on the distribution chart (Fig. 1) that all acute hearts have long Q-Tc intervals at any cardiac rate, and likewise that the quiescent hearts have short systoles Q-Tc at any cardiac rate. In addition, it is obvious that the duration of systole in acute cases is apparently uninfluenced by cardiac rate.

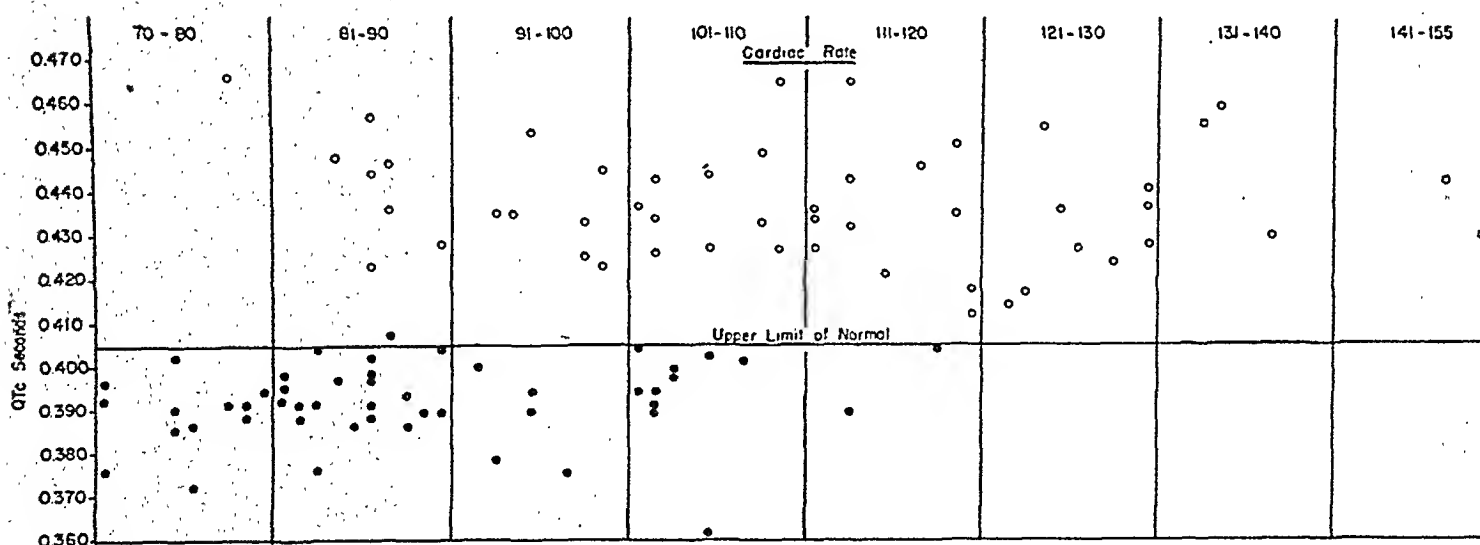


Fig. 1.—Duration of electrical systole in children with active and quiescent rheumatic fever in relation to cardiac rate. On this chart, fifty "active" and fifty "inactive" cases are distributed according to the Q-Tc of the patients at the time of observation and the cardiac rate at the same time.

The Ratio of Systole to Diastole $\frac{(Q-T)}{(T-Q)}$.—The physiologic principle that in normal hearts diastole is longer than systole is common knowledge. The ratio of the duration of systole to the duration of diastole is of the order of less than 1 up to the cardiac rate of 100. Table I shows that the $\frac{Q-T}{T-Q}$ quotient in the quiescent group of children is well within normal limits; that is, less than 1. Quotients slightly higher than 1 are found only among those with a cardiac rate above 100. Patients with acute carditis, on the other hand, have a markedly increased

$\frac{Q-T}{T-Q}$ quotient. The average quotient for this group is 1.463. None of these children have a quotient of less than 1 and a few have a quotient of more than 2.

It is clear from these observations that the duration of systole, both absolute and relative to diastole, is significantly longer in patients with acute carditis than in patients with quiescent rheumatic disease.

Relationship of $\frac{Q-T}{T-Q}$ Quotient to Cardiac Rate.—The physiologic principle that systole shortens less rapidly than diastole with increasing cardiac rate is also well known. This means that the $\frac{Q-T}{T-Q}$ quotient becomes greater with increasing cardiac rate. Our observation would seem to show that in patients with acute carditis the prolongation of systole relative to diastole follows this physiologic principle but at a significantly higher rate level; the $\frac{Q-T}{T-Q}$ quotient

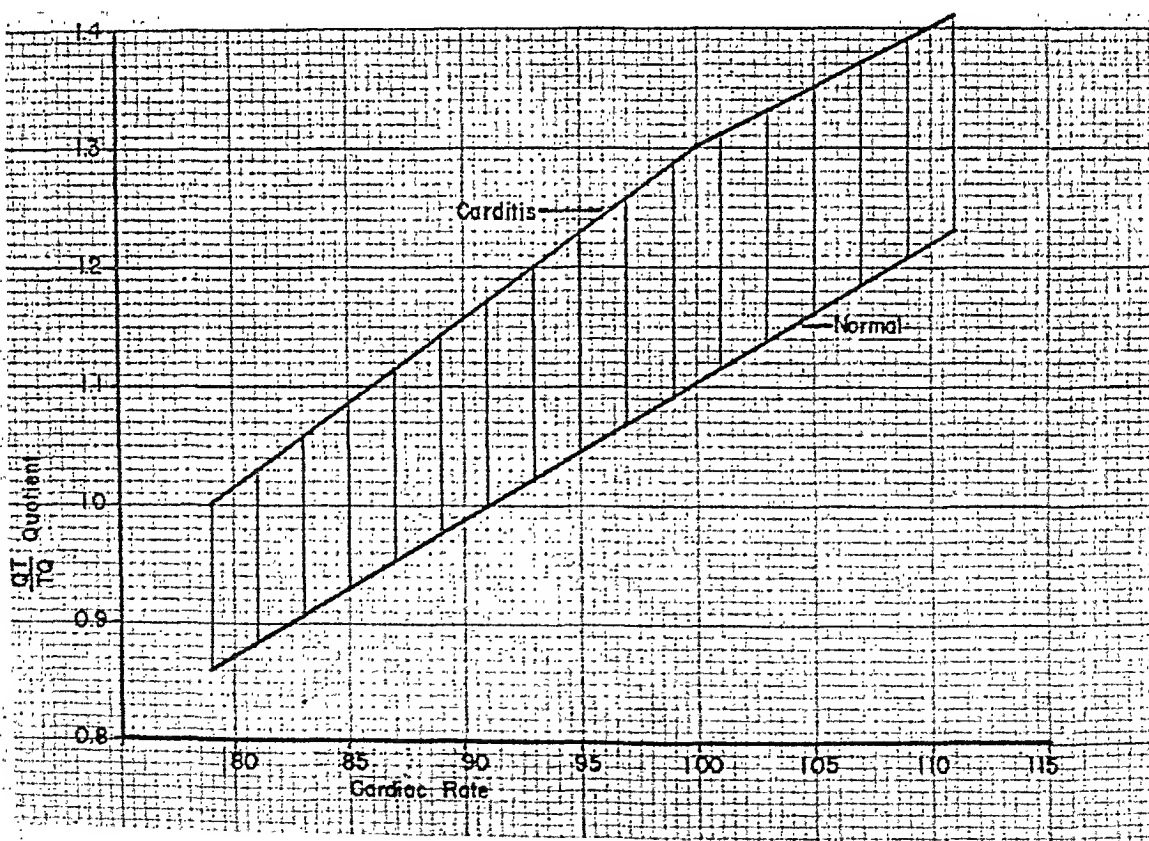


Fig. 2.—This represents the $\frac{Q-T}{T-Q}$ quotient of a child with acute carditis at different levels of cardiac rate. The line labeled normal represents the calculated quotients at corresponding rates on the basis of the upper limit of normal $Q-T_c$ of 0.405 second. The severity of carditis as judged by clinical observation of the patient was about the same at each rate. The parallelism of the two lines demonstrates that the prolongation of systole relative to diastole in acute carditis, as compared to normal, is uninfluenced by cardiac rate.

becomes greater with an increase in cardiac rate, but at a much higher heart rate than in children with quiescent hearts. Furthermore, in the presence of active carditis, this increasing quotient runs parallel to that found in children with normal (or quiescent) hearts provided the degree of carditis, as judged by the clinical course, is about the same at the various cardiac rates (Fig. 2).

It is clear from this observation that the difference in the magnitudes of the quotients in those with acute and quiescent hearts is not a function of cardiac rate. This would seem to predicate another factor which is responsible for the marked prolongation of systole relative to diastole that is found in acute carditis.

*Relationship of $\frac{Q-T}{T-Q}$ Quotient to Severity of Carditis.**—Examination of Table II shows that the $\frac{Q-T}{T-Q}$ quotient increases significantly with increase in severity of carditis. The average $\frac{Q-T}{T-Q}$ quotient in the group of children with the mildest grade of carditis (1 plus) was 1.257 as compared with 1.825 in the group with the severest form of carditis (4 plus). Table II also shows that the difference between the $\frac{Q-T}{T-Q}$ quotient of acute cases and that of the calculated quotient for comparable cardiac rate rises with the increase in severity of the carditis. That the

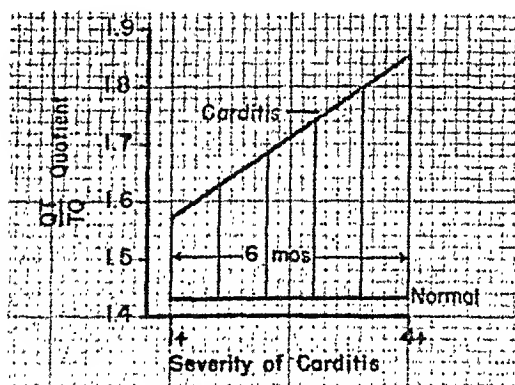


Fig. 3.—This illustrates the $\frac{Q-T}{T-Q}$ quotient of a child who was admitted with mildly "active" rheumatic disease but whose activity increased in severity over a period of six months. The quotient 1.85 was calculated from the cardiogram taken shortly before the child died of acute pancarditis. The cardiac rate at the highest and the lowest quotients was the same, 125. The line labeled normal represents the calculated quotient at a rate of 125 with a Q-Tc of 0.405 second.

*For many years patients at St. Francis Sanatorium suffering from rheumatic carditis have been graded according to the following criteria:

- 1 plus severity: Patients who present laboratory evidence of rheumatic activity and, in addition, present the clinical criteria of cardiac involvement; that is, changing heart sounds and murmurs, labile cardiac rate, and fatigability.
- 2 plus severity: Patients who, in addition to the foregoing findings, show definite cardiographic evidence of conduction disturbance or/and changes in the ventricular complexes.
- 3 plus severity: Patients, who, in addition to the foregoing, present a tumultuous heart with moderate symptoms of impaired cardiac reserve.
- 4 plus severity: Patients with acute pancarditis.

TABLE II. DURATION OF SYSTOLE BOTH ABSOLUTE AND RELATIVE TO DIASTOLE IN RELATION TO DEGREE OF SEVERITY OF CARDITIS

1	2	3	4	5	6	7
RATE	Q-T	Q-T UPPER LIMIT OF NORMAL	Q-Tc	$\frac{Q-T}{T-Q}$	$\frac{Q-T}{T-Q}$ UPPER LIMIT OF NORMAL	DIFFERENCE CLMS 5-6
<i>Carditis 1 Plus Severity</i>						
102	0.3280	0.3116	0.426	1.17	1.130	0.040
113	0.3144	0.2950	0.432	1.31	1.250	0.060
98	0.3484	0.3170	0.435	1.14	1.068	0.070
97	0.3340	0.3200	0.425	1.15	1.060	0.090
123	0.2920	0.2846	0.418	1.49	1.390	0.100
86	0.3580	0.3390	0.423	1.05	0.940	0.110
115	0.3028	0.2920	0.420	1.39	1.280	0.110
111	0.3150	0.2980	0.428	1.36	1.230	0.130
Av. 105	0.3240	0.3071	0.4252	1.257	1.168	0.0880
<i>Carditis 2 Plus Severity</i>						
93	0.3480	0.3230	0.435	1.17	0.990	0.180
94	0.3484	0.3227	0.435	1.20	1.010	0.190
126	0.2960	0.2814	0.427	1.64	1.450	0.190
105	0.3200	0.3080	0.421	1.37	1.170	0.200
107	0.3244	0.3045	0.433	1.39	1.190	0.200
87	0.3720	0.3370	0.447	1.16	0.950	0.210
111	0.3192	0.2980	0.435	1.45	1.230	0.220
111	0.3200	0.2980	0.436	1.45	1.230	0.220
101	0.3392	0.3130	0.438	1.34	1.110	0.230
84	0.3800	0.3420	0.449	1.16	0.920	0.240
Av. 102	0.3367	0.3127	0.4356	1.333	1.125	0.2080
<i>Carditis 3 Plus Severity</i>						
125	0.3024	0.2826	0.436	1.69	1.430	0.260
86	0.3864	0.3398	0.457	1.22	0.940	0.280
95	0.3620	0.3214	0.455	1.32	1.030	0.290
105	0.3400	0.3080	0.444	1.46	1.170	0.290
102	0.3488	0.3116	0.453	1.45	1.130	0.320
113	0.3212	0.2950	0.443	1.57	1.250	0.320
107	0.3400	0.3045	0.450	1.54	1.190	0.350
Av. 119	0.3429	0.3088	0.4482	1.464	1.157	0.3014
<i>Carditis 4 Plus Severity</i>						
129	0.3016	0.2780	0.441	1.86	1.460	0.400
118	0.3212	0.2888	0.451	1.72	1.310	0.410
134	0.3144	0.2700	0.471	1.99	1.550	0.440
108	0.3472	0.3020	0.466	1.67	1.194	0.476
113	0.3412	0.2950	0.466	1.76	1.230	0.530
124	0.3200	0.2837	0.455	1.95	1.400	0.550
Av. 120	0.3242	0.2862	0.4583	1.825	1.357	0.5676

1, Cardiac rate; 2, measured Q-T interval; 3, Q-T interval calculated on basis of 0.405 (upper limit of normal); 4, corrected Q-T interval; 5, quotient calculated from measured Q-T interval; 6, quotient calculated from column 3.

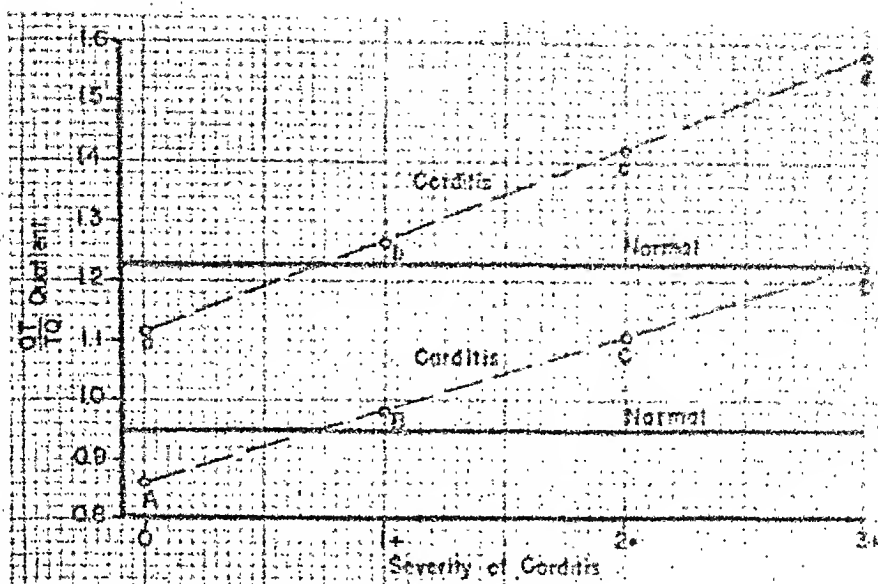
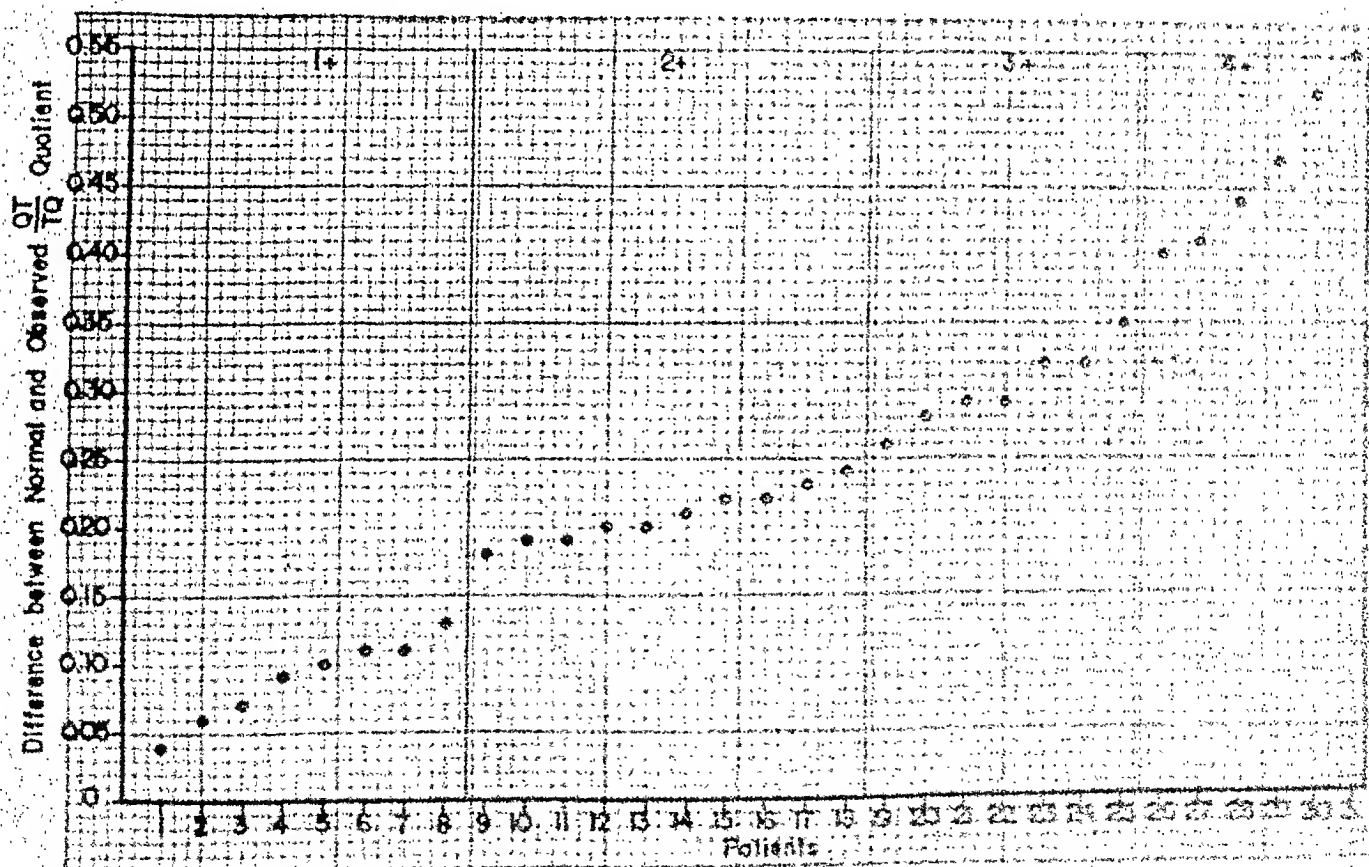


Fig. 4.—This represents the $\frac{Q-T}{T-Q}$ quotients of eight rheumatic children. A was equivalent with a cardiac rate of 86. B, C, and D had acute carditis with the same cardiac rate as A. Cases B, C, and D represent children with a cardiac rate of 111 but with a degree of carditis corresponding to that in A, B, C, and D.



increase in quotient is absolute and not influenced by rate is well illustrated in Figs. 3 and 4. This finding was common in all our patients with acute carditis when studied in this manner (Fig. 5). Furthermore it was observed that as the severity of carditis increases in the same patient, the $\frac{Q-T}{T-Q}$ quotient rises accordingly, and as carditis subsides, the reverse is the case. This is uninfluenced by cardiac rate (Figs. 6 and 7).

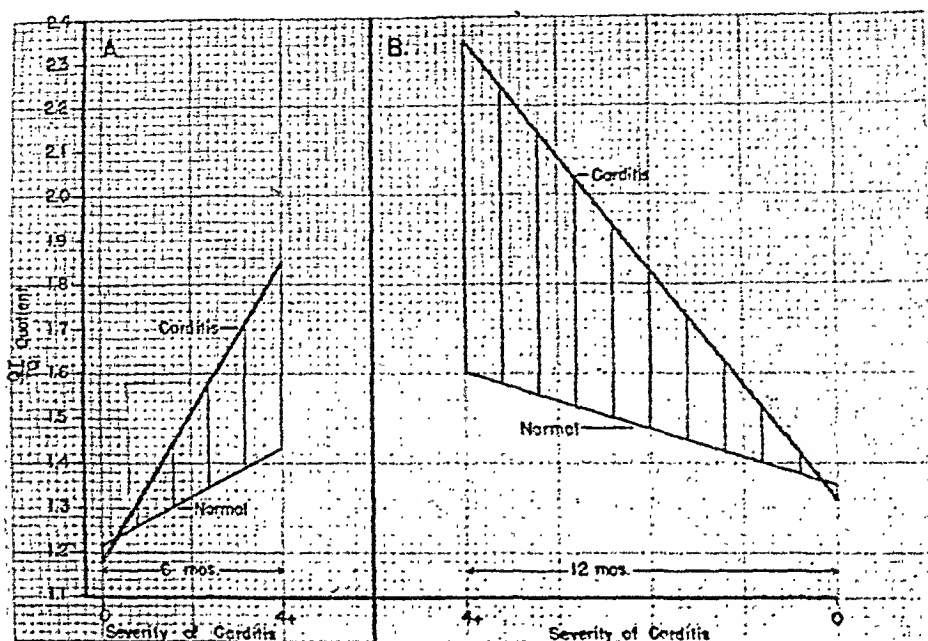


Fig. 6.—A represents a patient whose $\frac{Q-T}{T-Q}$ quotient was studied from quiescence to the end of a fulminating pancarditis. B represents a patient who was admitted with a severe carditis and recovered. The lines labeled normal represent a calculated quotient at corresponding cardiac rates with a maximum normal Q-Tc of 0.405 second.

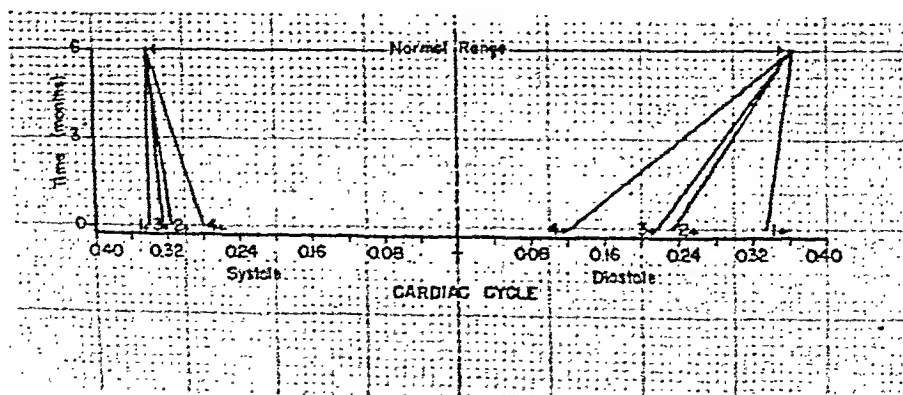


Fig. 7.—This chart represents the duration of systole relative to diastole of four patients with acute carditis of different degrees of severity. These were followed until quiescence, at which time they all had a Q-Tc of 0.400 and a rate of 86.

COMMENT

The diagnosis and evaluation of cardiac involvement during the course of the acute stage of rheumatic disease has been one of the trying problems in medicine for many years. In recent years much has been learned from electrocardiographic studies regarding the occurrence and extent of cardiac damage in rheumatic fever. Criteria for recognition and evaluation of impairment of the integrity of the heart muscle during the course of acute carditis, however, have not been forthcoming. The physiologic principle that the disturbance in the normal time sequence of events in the cardiac cycle is significant of an impaired heart muscle has not been fully explored by clinicians in the study of rheumatic carditis.

The observations presented in this paper seem to indicate that a distinct disturbance of cardiodynamics is present in acute carditis and that this disturbance is mirrored in the abnormal relationship of the duration of systole relative to diastole. The apparent inversion of the normal time sequence of events in the cardiac cycle is a constant finding in cases of acute carditis. In addition, we have found this abnormal sequence helpful in evaluating the degree of impairment of the functional integrity of the heart muscle. The degree of severity of carditis as measured by clinical observation of the patient and the extent of disturbance in the time relationship of systole relative to diastole run almost exactly parallel in our group of cases.

Our findings, furthermore, would seem to add a more direct method for studying the duration of rheumatic activity. Those patients who are considered to have subclinical rheumatic activity show a significant cardiodynamic disturbance. As long as this disturbance in the normal time sequence of events in the cardiac cycle is found, the presence of rheumatic activity should be suspected. Our experience with these children teaches that those who show an abnormal prolongation of the duration of systole relative to diastole do poorly when treatment is terminated even when all other laboratory criteria are normal. We are also impressed from these studies that few, if any, children having rheumatic disease escape active impairment of the integrity of the heart muscle during the course of the acute stage of the disease.

Finally, our observations point the way to a better evaluation of the effect of various forms of therapy used in acute carditis. Bed rest, salicylates, digitalis, diuretics, oxygen, and other forms of treatment now employed in acute carditis can be studied in relation to the extent and duration of acute cardiac involvement. These studies are now in progress.

SUMMARY AND CONCLUSIONS

1. One hundred boys and girls from 7 to 14 years of age were observed under controlled conditions—fifty during an attack of acute carditis and fifty during a long period of quiescence.

2. The duration of electrical systole (Q-T) both absolute and relative to diastole was studied in these children in relation to cardiac rate and severity of carditis.

3. The observation was made that the duration of electrical systole (Q-T) both absolute and relative to diastole is significantly prolonged in all cases of acute carditis.

4. This prolongation was found to be a function of the severity of the carditis and not of the cardiac rate.

5. It is postulated that this disturbance in the normal sequence of events in the cardiac cycle is characteristic of acute carditis and adds a valuable diagnostic criterion for the recognition of rheumatic carditis and an electrocardiographic method for following the progress of carditis.

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ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH METHYL ALCOHOL POISONING

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THE toxicity, pathologic findings, and treatment of methyl alcohol poisoning are well known and have been reviewed by Voegtlin and Watts,¹ Jacobson, Russell, Grimm, and Fox² and Kaplan and Leverault.³ Electrocardiographic changes, however, are not mentioned in these reviews, and a survey of the literature reveals only one case report⁴ in which electrocardiographic changes were demonstrated. Furthermore, no mention of electrocardiographic abnormalities associated with wood alcohol poisoning is made in standard medical textbooks. The following report deals with eight cases of methyl alcohol poisoning in which electrocardiographic studies were undertaken.

CASE MATERIAL

Nine men accidentally ingested various quantities of methyl alcohol from an unmarked container under the assumption that it was grain alcohol. The alcohol was diluted approximately one part in three with water, and the amounts ingested varied from five to six large cupfuls to a few sips. The exact amounts ingested could not be ascertained accurately. All were admitted to the hospital two days later. One man died about forty-eight hours after drinking this mixture and one became blind. The others recovered entirely.

Headache, nausea, vomiting, blurring of vision, scotomas, weakness, myalgia, and lassitude were common complaints in all and existed in varying degrees of severity. Of the eight patients who survived, two appeared seriously ill on admission, one of the men being semicomatose. Two of the patients appeared mildly ill and the remainder had only minor complaints. Hyperpnea and râles in the lung bases were noted in three of the men and cyanosis in two. Otherwise the physical findings were not striking. Six patients had a positive test for acetone in the urine.

Treatment consisted of parenteral fluids, sodium bicarbonate by mouth, Ringer-lactate solution intravenously, and liver extract intramuscularly. Four of the patients received small doses of insulin with large amounts of glucose. The most seriously ill patients received plasma.

Electrocardiograms were taken twelve hours after admission, five days after treatment had been instituted, and again eleven days after admission.

RESULTS

Seven of the eight cases showed definite electrocardiographic changes which reverted toward normal following treatment (Table I). Five showed marked abnormalities and two showed changes of lesser degree. One man had a normal electrocardiogram except for slight prolongation of the Q-T interval. Electro-

TABLE I. ELECTROCARDIOGRAPHIC FINDINGS AFTER INGESTION OF METHANOL

CASE	RELATIVE ESTIMATED AMOUNTS OF METHANOL INGESTED	CLINICAL APPEARANCE	ECG TWELVE HOURS AFTER ADMISSION	ECG FIVE DAYS AFTER TREATMENT	ECG ELEVEN DAYS AFTER TREATMENT
1	++++	Seriously ill	Low voltage T in Leads I and II; T ₃ isoelectric	Increased voltage of T in Leads I, II, and III	No change from previous tracing
2	±	Appeared normal	Normal except for slight prolongation of Q-T interval	No change	No change from previous tracing
3	++++	Appeared normal	Low voltage T in Leads I, II, and III; T in CF ₁ diphasic	Increased voltage of T in Leads I, II, and III; T in CF ₄ no longer diphasic	Further increase in voltage of T in Leads II and III
4	++++	Appeared normal	Low voltage T in Leads I and II; T ₃ diphasic	T ₁ increased in voltage	T ₂ increased in voltage
5	++	Appeared normal	Low voltage T in Leads I, II, III, and CF ₁	Increased voltage T in Leads I, II, and CF ₄ ; amplitude of T ₃ decreased and QRS notched in CF ₄	Further increase in voltage of T ₂ and T ₃ ; QRS no longer notched in CF ₁
6	++++	Mildly ill	Record within normal limits; T ₃ inverted	T ₂ slightly increased in voltage; T ₃ upright	Increased voltage of T ₃
7	+++	Mildly ill	Low voltage T ₁ and T ₂	T ₂ increased in voltage	Increased voltage of T ₁ and T ₂
8*	++++	Seriously ill	Low voltage T ₁ and T ₂	Increased voltage of T ₁ and T ₂ ; T ₃ now inverted	Further increase in voltage of T ₁ and T ₂

*Developed amblyopia.

cardiograms taken eleven days after admission showed continuing changes in the same direction in six of the patients.

The most frequent finding was low voltage of the T waves in Leads I and II which reverted toward normal after treatment (Figs. 1 and 2). Increased voltage of the T waves in Lead III and in CF₄ following treatment were noted in several of the patients (Table I). Minor changes in the QRS complex also occurred.

The Q-T interval as determined by the formula $K = \frac{QT^*}{\sqrt{RR}}$ was found to be slightly prolonged in four patients (Table II).

TABLE II. DURATION OF Q-T INTERVALS

CASE	BEFORE TREATMENT (SEC.)	FIVE DAYS AFTER TREATMENT (SEC.)	ELEVEN DAYS AFTER TREATMENT (SEC.)
1	.39	.39	.41
2	.40	.39	.40
3	.38	.38	.40
4	.39	.395	.39
5	.36	.37	.38
6	.37	.38	.38
7	.40	.40	.395
8	.36	.36	.36

COMMENT

The electrocardiographic changes which occurred in these patients are comparable to those found in the patient reported on by Merritt and Brown.⁴ In their patient, however, a normal electrocardiogram was found on admission and changes did not occur until four days after the ingestion of the poison and twenty-four hours after treatment had been instituted. The findings in our patients were present about sixty hours after the men had partaken of the methyl alcohol.

Somewhat similar changes, including prolongation of the Q-T interval, were found by Bellet and Dyer⁵ in seventeen patients with diabetic acidosis. However, here too, the electrocardiographic changes did not occur until twenty-four hours after treatment had been instituted. S-T segment depression also occurred in their patients but was not present in ours. Both Merritt and Brown⁴ and Bellet and Dyer⁵ attribute the electrocardiographic changes to delayed myocardial damage occurring as the result of acidosis.

The oxidation of methyl alcohol results in an acidosis due to the formation of formic acid and formaldehyde. Unfortunately, determinations of the carbon dioxide combining power were not available in these patients, but it is safe to

*Bazetts' formula corrected for Q-T interval. K is a constant. R-R is the cycle length.

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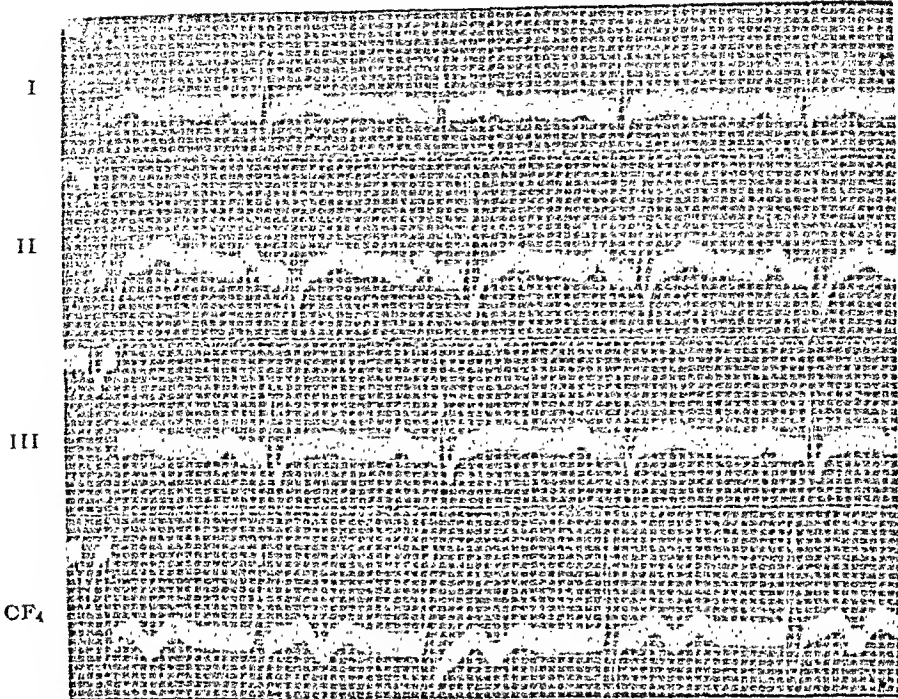


Fig. 1A.—Case 3. Electrocardiogram twelve hours after admission. Low voltage of T waves in Leads I, II, and III. T in CF₄ is slightly diphasic. Prominent U waves are present in CF₄.

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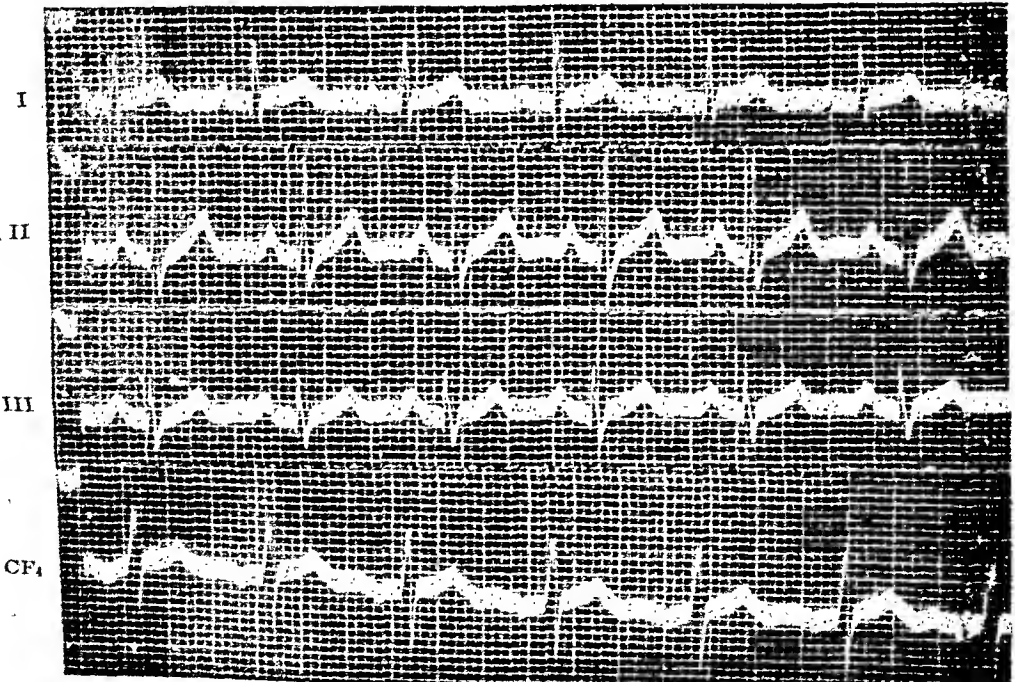


Fig. 1B.—Case 3. Electrocardiogram after treatment. T waves in Leads I, II, and III have increased in amplitude. T in CF₄ no longer diphasic.

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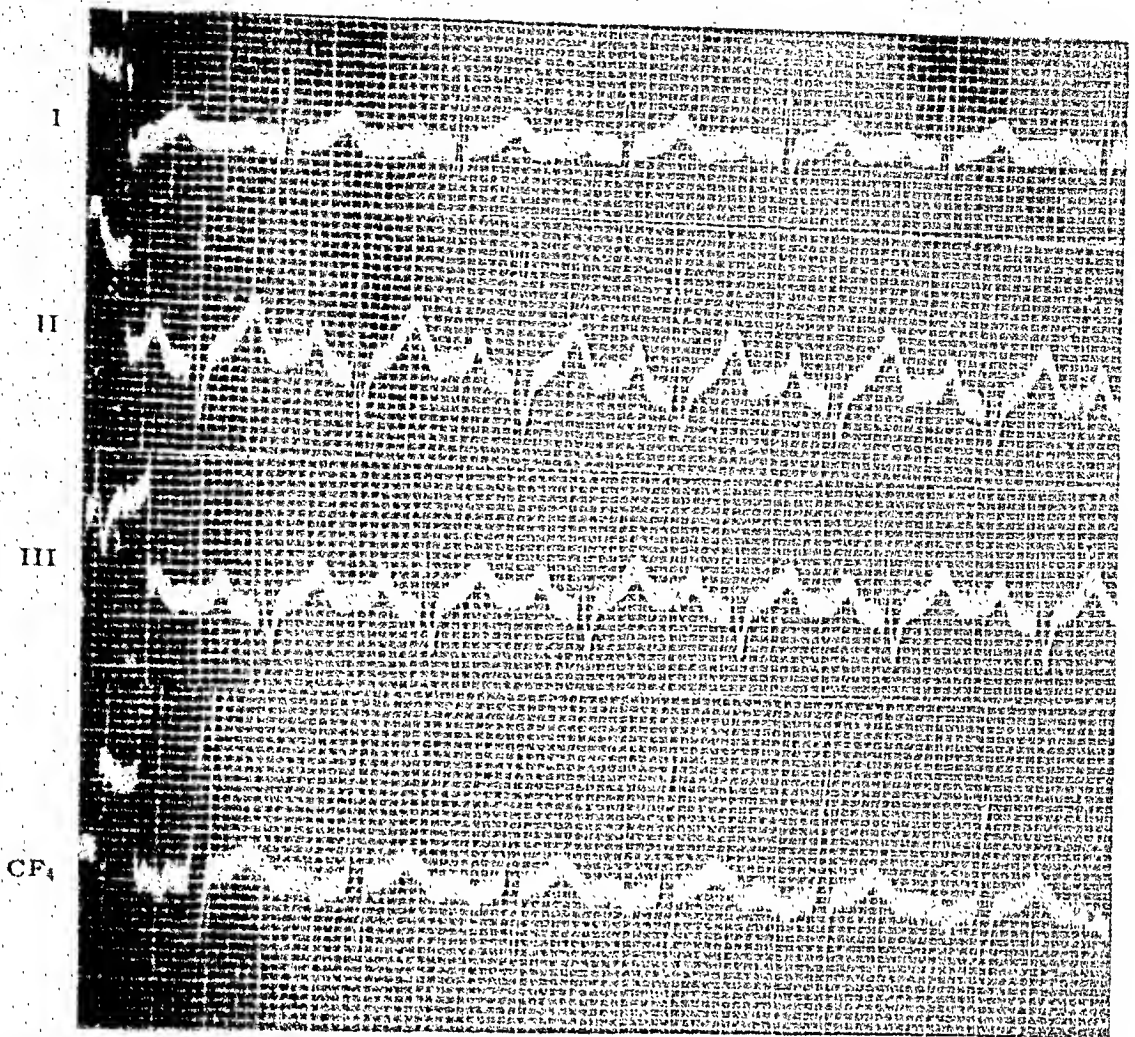


Fig. 1C.—Case 3. Electrocardiogram eleven days after treatment shows further increase in voltage of T waves in Leads II and III.

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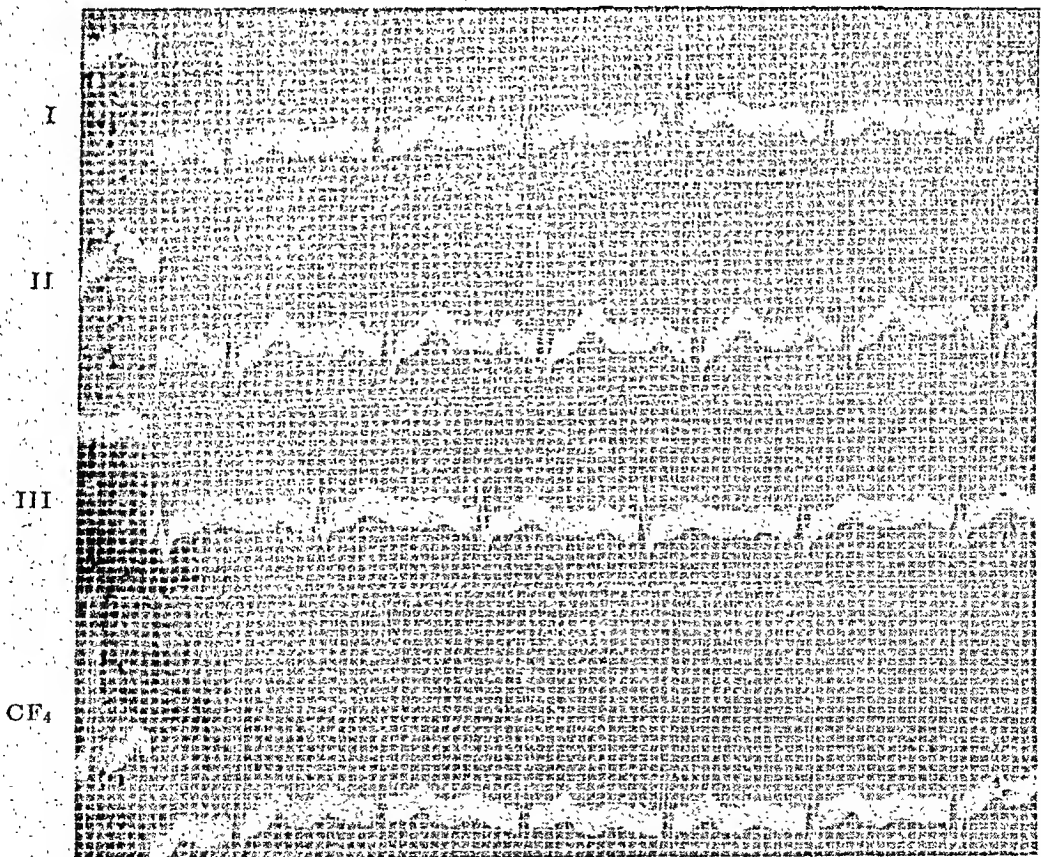


Fig. 2A.—Case 5. Electrocardiogram twelve hours after admission. Low voltage of T waves in Lead I and in CF4.

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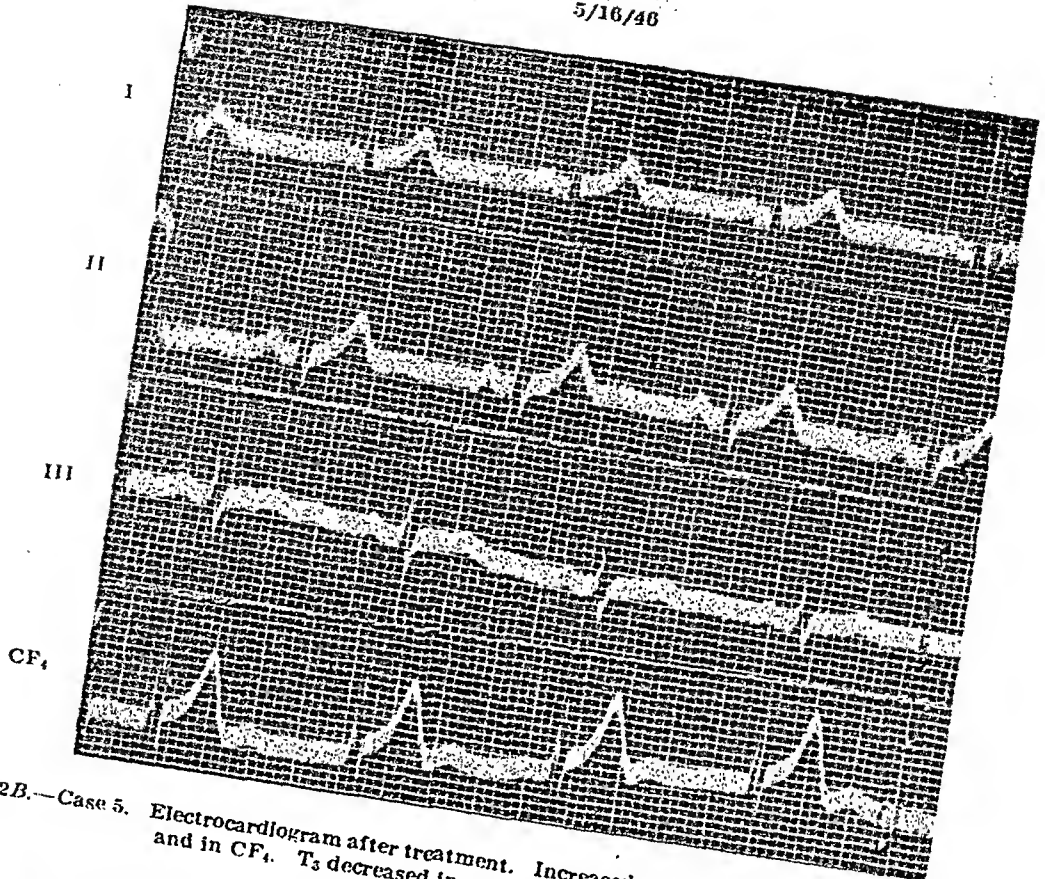


Fig. 2B.—Case 5. Electrocardiogram after treatment. Increased voltage of T waves in Leads I and II, and in CF₄. T₃ decreased in voltage and QRS notched in CF₄.

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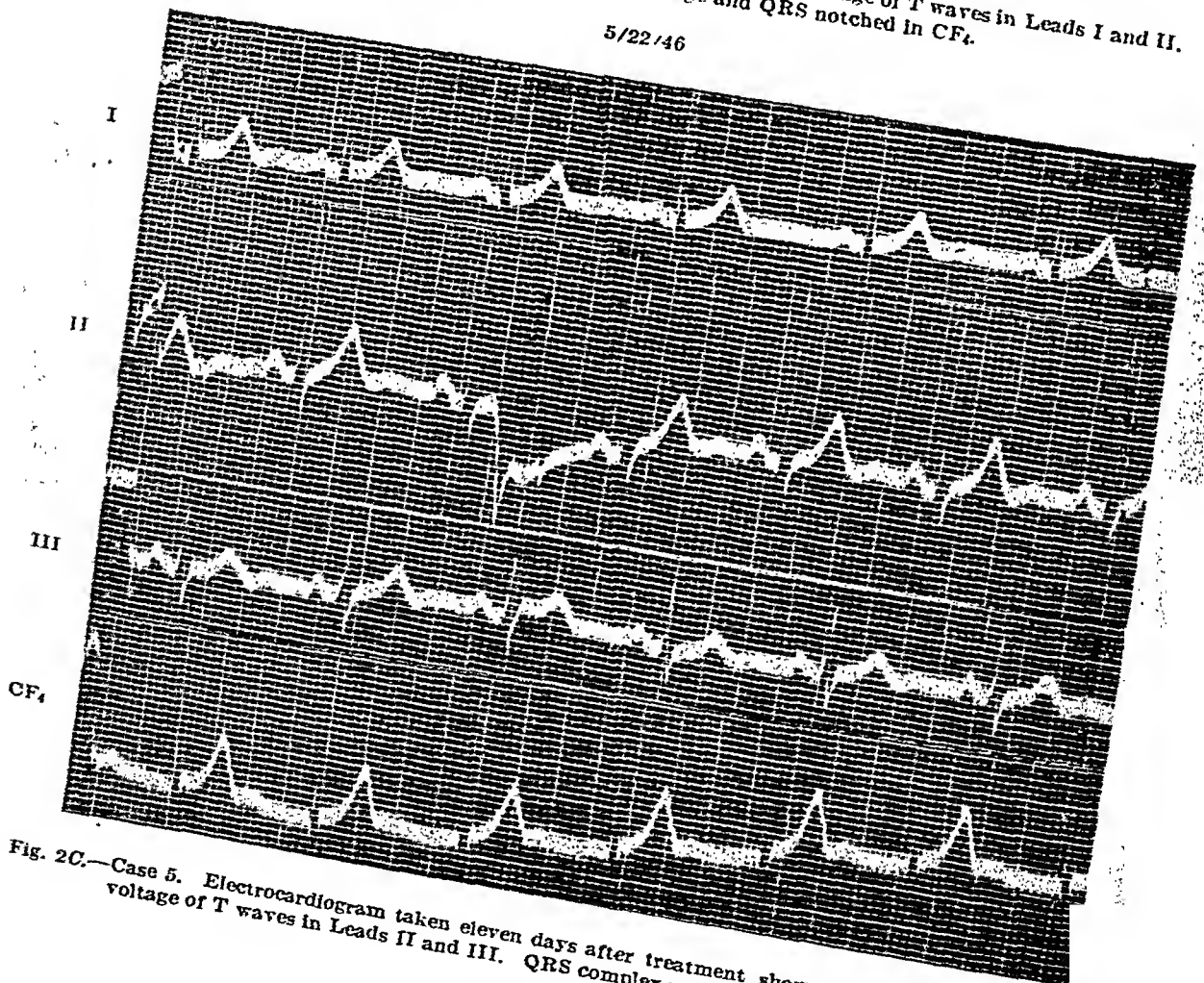


Fig. 2C.—Case 5. Electrocardiogram taken eleven days after treatment shows further increase in voltage of T waves in Leads II and III. QRS complex no longer notched in CF₄.

assume that they were probably suffering from acidosis at the time of admission. However, methyl alcohol, formic acid, and formaldehyde are all toxic substances, per se, and the possibility of direct myocardial toxicity cannot be ruled out entirely.

No direct correlation could be drawn between the degree of electrocardiographic change and the estimated amount of methanol ingested. The patient (Case 2), however, who showed no change except slight prolongation of the Q-T interval, took the least amount of alcohol. It was the clinical impression that habituation to alcohol exerted a protective influence.

The Q-T intervals were found to be only slightly prolonged and were not significantly altered following treatment. No correlation could be drawn between the amount of electrocardiographic changes which occurred and the duration of the Q-T interval.

SUMMARY AND CONCLUSIONS

1. Electrocardiographic changes were found in seven of eight patients with methyl alcohol poisoning.
2. The most common finding was decrease in voltage of the T waves in Leads I and II.
3. Slight prolongation of the Q-T interval was present in four patients but did not appear to be significant.
4. The electrocardiograms reverted toward normal after treatment.
5. The cause of the electrocardiographic changes is not known but may be due to acidosis or to the direct effect of methyl alcohol or its metabolites on the myocardium.

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ATRIONODAL RHYTHM WITH VENTRICULAR BIGEMINY

REPORT OF A CASE WITH UNUSUAL MECHANISM

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RARELY a dominant atrionodal rhythm is complicated by ventricular bigeminy. This irregularity is of particular interest because of the wide variety of mechanisms by means of which the second beat of the pair might be linked with the first. The explanation for the coupling in some cases is obvious, in others obscure, and, in still others, entirely speculative. After a thorough search of the literature, the following list of mechanisms which might result in atrionodal bigeminy was compiled:

1. Atrionodal beats coupled with premature sinus,¹ auricular, nodal,² or ventricular² contractions
2. Reciprocal rhythm^{3,4}
 - A. With retrograde conduction to auricles
 - B. With reciprocal pathway limited to A-V node^{4,5}
3. Auricular parasystole with interference dissociation^{6,7}
4. Nodal escape beats paired with sinus beats⁸ (pseudoreciprocal rhythm⁹)
 - A. With sinus nodal pacemaker in normal location
 - B. With sinus nodal pacemaker outside of normal location¹⁰
5. Nodal escape beats paired with auricular escape beats⁵
6. Nodal escape beats paired with nodal extrasystoles
 - A. Without independent auricular rhythm¹¹
 - B. With independent auricular rhythm and interference dissociation²
7. Normal supraventricular beats interpolated upon a dominant A-V nodal rhythm^{12,13}
8. A dominant A-V nodal rhythm, paired with sinus nodal or auricular beats, which are mechanically stimulated by the contracting ventricle¹⁴

In this paper we describe an unusual example of atrionodal rhythm with ventricular bigeminy which was characterized by the following rhythmic sequences: (1) ventricular complex of atrionodal origin; (2) antegrade, abnormal P wave; (3) normal, or aberrant, QRS complex. The coupling between the first ventricular beat and the auricular beat, or between the two ventricular beats, was fixed. Although we cannot explain the mechanism precisely, we believe the theoretical implications are of sufficient interest to warrant placing this case on record.

From the Cardiac Clinic of the Newark, N. J. Health Department.
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CASE REPORT

J. McN., a 56-year-old Negro woman, was first referred to the Cardiac Clinic in September, 1940, because of dyspnea, palpitation and substernal pain on exertion, and dizziness. She admitted a past history of syphilis, for which she had received adequate treatment from 1935 to 1938. The heart beat was regular, the rate 60 per minute, and the blood pressure was 160/90. The heart was enlarged moderately to the left, and a faint, harsh systolic murmur was audible over the aortic area.

She was again referred for study in August, 1944. Because of a history of dizziness, staggering, and syncope, and the presence of a bradycardia, it was suspected that she might be suffering from the Adams-Stokes syndrome. The physical examination revealed no essential change, except that her blood pressure had risen to 175/120. No disturbances of rhythm or conduction were demonstrated by the electrocardiogram.

It was not until one year later, Aug. 2, 1945, that an arrhythmia was first detected. On this date, and on frequent occasions during the next few months, a bigeminal rhythm was present. The dominant rhythm was slow, at a rate of from 18 to 23 per minute. The bigeminy was unusually persistent and could not be terminated by such influences as deep breathing, change of posture, exercise, occluding or carotid sinus pressure, nitroglycerine, or intravenous atropine sulfate. At no time had digitalis been administered.

Laboratory study revealed the following: The blood count and the blood sugar and urea nitrogen concentrations were normal. Urinalysis was negative except for a trace of albumin. The erythrocyte sedimentation rate was 44 mm. in one hour. The blood Wassermann reaction was negative. A teleroentgenogram of the chest showed moderate left ventricular hypertrophy and dilatation, a normal vascular shadow, and clear lung fields. Frequent electrocardiograms, which will be analyzed in detail, disclosed the presence of an atrionodal rhythm with ventricular bigeminy.

The diagnosis was as follows: Hypertensive and arteriosclerotic heart disease, left ventricular hypertrophy and dilatation, coronary artery sclerosis, atrionodal and idioventricular rhythm with ventricular bigeminy, anginal syndrome. It was thought that she might also have syphilitic aortitis with coronary ostial stenosis.

The patient developed symptoms of mental deterioration and in September, 1945, was committed to the Greystone Park Sanitarium. The psychiatric diagnosis was cerebral arteriosclerosis with psychosis.

ANALYSIS OF ELECTROCARDIOGRAMS

Frequent electrocardiograms were obtained. The tracing in Fig. 1 (Aug. 23, 1945) is illustrated in order to demonstrate the usual pattern of the various complexes for this patient. Sinus bradycardia was present, with a rate of 56 per minute. The P-R interval was 0.24 second in duration. The electrical axis was deviated to the left. The QRS complexes were slurred as they rounded into elevated RS-T segments in Leads II and III. The precordial leads, CF_1 to CF_6 inclusive, were not remarkable, except for similar slurring of the QRS complexes. This tracing did not differ materially from the first one made in September, 1940, except for the slight prolongation of A-V conduction present in the last tracing.

On five occasions a bigeminal rhythm was recorded, and it is with an analysis of these tracings that we are particularly concerned. Electrocardiograms which appear in Fig. 2 were taken Aug. 2, 1945. In Lead Ia, the third and fourth beats were of normal sinus origin. The P-R interval was 0.17 second. The RS-T

segments were slightly depressed. The first, fifth, and seventh ventricular complexes of Leads Ia and the first, third, fifth, and seventh complexes of Lead Ib were of atrionodal origin. They differed only slightly in contour from the normal sinus beats, with the exception of the fifth ventricular complex in Lead Ia, which was markedly aberrant due to defective conduction in the right bundle branch. Each of the atrionodal beats was coupled with a supraventricular beat of unknown origin (second, sixth, and eighth in Lead Ia and the second, fourth, sixth, and eighth ventricular beats in Lead Ib), which differed slightly in contour from both the normal sinus and atrionodal beats. An auricular complex was present between each pair of ventricular beats. This P wave was aberrant. It was

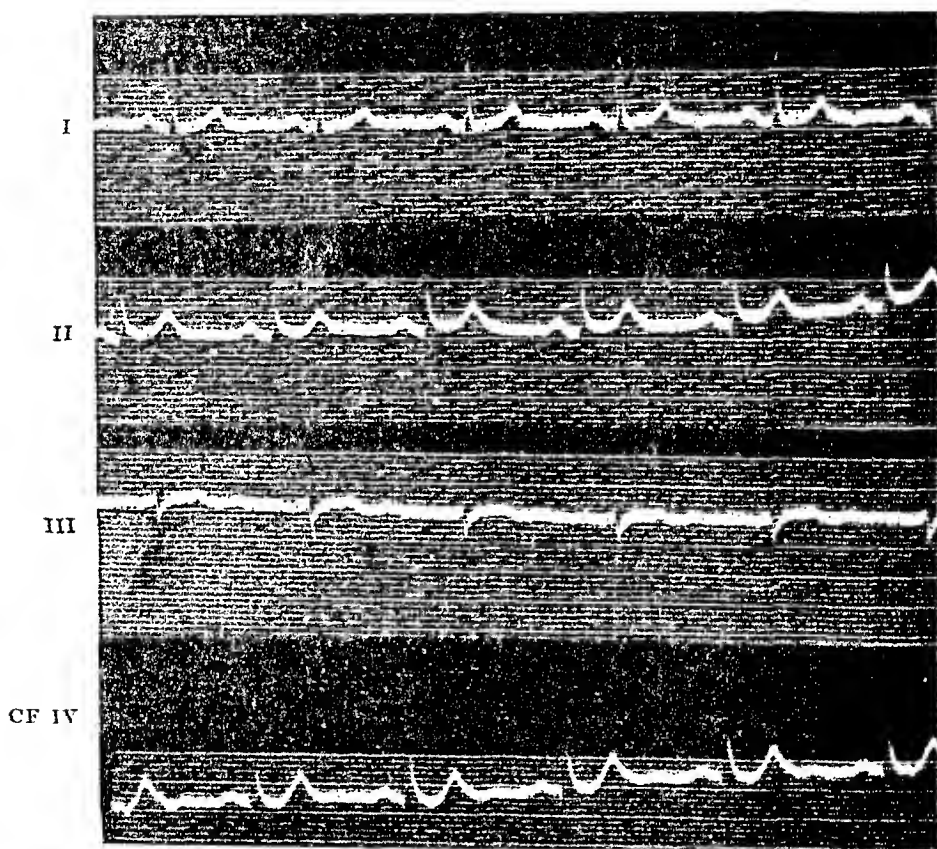


Fig. 1.—Aug. 23, 1945.

upright but of lower voltage than normal. The P wave fell quite uniformly on the same phase of ventricular systole: on the descending limb of the preceding T wave. An exception is the first P wave in Ib, which was found on the upstroke of the T wave and was followed by an aberrant QRS response after a prolonged P-R interval. With the exception of this pair, and the second pair in Ia, the coupling was fixed; the interval between two successive complexes was 0.67 second. The interval between dominant atrionodal beats varied from 2.62 to 3.28 seconds, corresponding to rates of 23 to 18 per minute. Since this rate was



Fig. 2.—Aug. 2, 1945.

much slower than the usual rate of an A-V nodal rhythm, it is probable that either the A-V node was markedly depressed, along with other automatic centers, or that the interpolation of the coupled beat temporarily depressed the A-V nodal pacemaker. The latter explanation is more likely correct since on other occasions when two independent A-V nodal beats occurred in succession, the interval was 1.16 seconds in duration, corresponding to a rate of 51 per minute.

The third and eighth cycles of IIa and the fifth and sixth cycles of IIb were of normal sinus origin. The P-R interval varied from 0.20 to 0.24 second. A-V nodal beats appeared at the following positions: the first beat in IIa and the third in IIb. The fourth and sixth ventricular beats in IIa and the first and seventh in IIb were idioventricular in origin. Both the A-V nodal and idioventricular beats were coupled in each instance with a second ventricular beat, and a P wave appeared between the two. The P wave in this lead, also, was upright and slightly aberrant. The couplets dominated by A-V nodal beats showed an R-R interval identical with that in Lead I, while in the couplets which were introduced by idioventricular beats, the R-R interval was prolonged to from 0.76 to 0.80 second. The interval between dominant idioventricular beats was 3.44 seconds, corresponding to an inherent rate of 17 per minute.

Leads III and IV repeated the same general trend as Leads I and II and are not shown in this illustration. P_3 was inverted.

On Aug. 9, 1945, an unusually persistent bigeminal rhythm occurred (Figs. 3A and 3B). On this date ninety-seven couplets were registered, and the first seventy-one were in sequence until a single interposed sinus beat interrupted this mechanism (Fig. 3A, Lead III). The R-R cycle length of the dominant rhythm varied from 2.28 to 2.47 seconds, but the coupling was constant at 0.57 second. The P waves again were aberrant and also differed in contour from analogous beats in Fig. 2 and indicated a slightly different focus of origin. The second QRS complex of each couplet was abnormal in appearance and widened to 0.12 second; this aberrance indicated functional block in the right bundle branch. In Fig. 3B a portion of Lead II is shown. This is a continuous tracing which illustrates the fixed coupling despite variations in the interval between the second beat of the couplet and the next dominant atrionodal beat.

On three other occasions a prolonged bigeminal rhythm was recorded. The bigeminy was not interrupted by change in posture, exercise, deep breathing, or oculobulbar or carotid sinus pressure. On one occasion, while a bigeminal rhythm was in progress, 0.0013 Gm. of atropine sulfate was administered intravenously with interesting consequences (Fig. 4). In the control record, the R-R interval of the dominant nodal rhythm varied from 2.40 to 2.43 seconds. The coupling interval was 0.60 second. One minute after the injection of atropine sulfate, a triple rhythm appeared. The first ventricular beat of each triplet was of atrionodal origin, the second beat was similar to that in the control and showed aberrant conduction, while the third ventricular beat was preceded by an abnormal P wave with a short interval of 0.08 second. When triplets occurred on other occasions in Lead II, the P wave preceding the third ventricular element was also upright. Therefore, this beat may be an auricular extrasystole. The

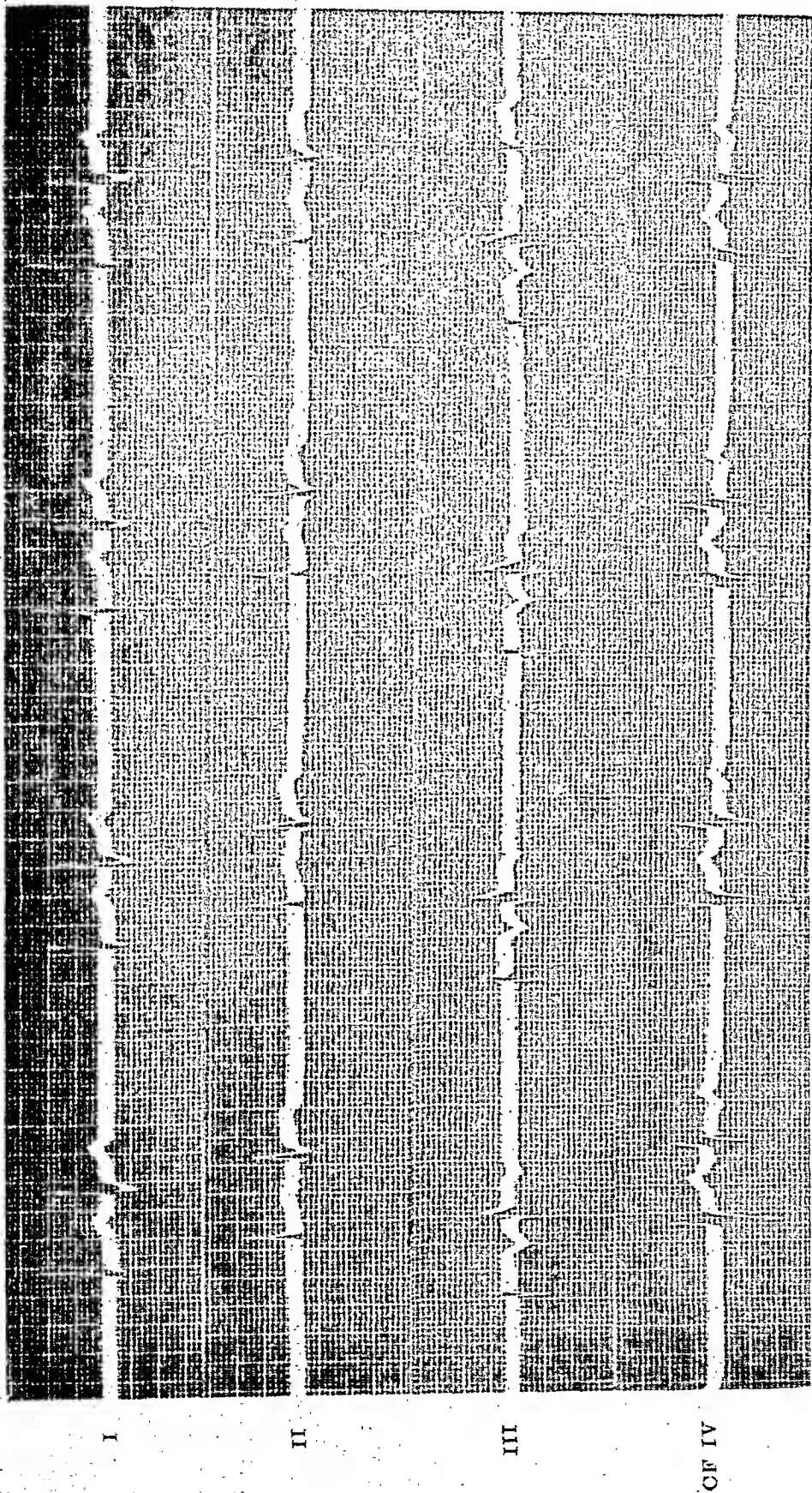


Fig. 3A.—Aug. 9, 1945.

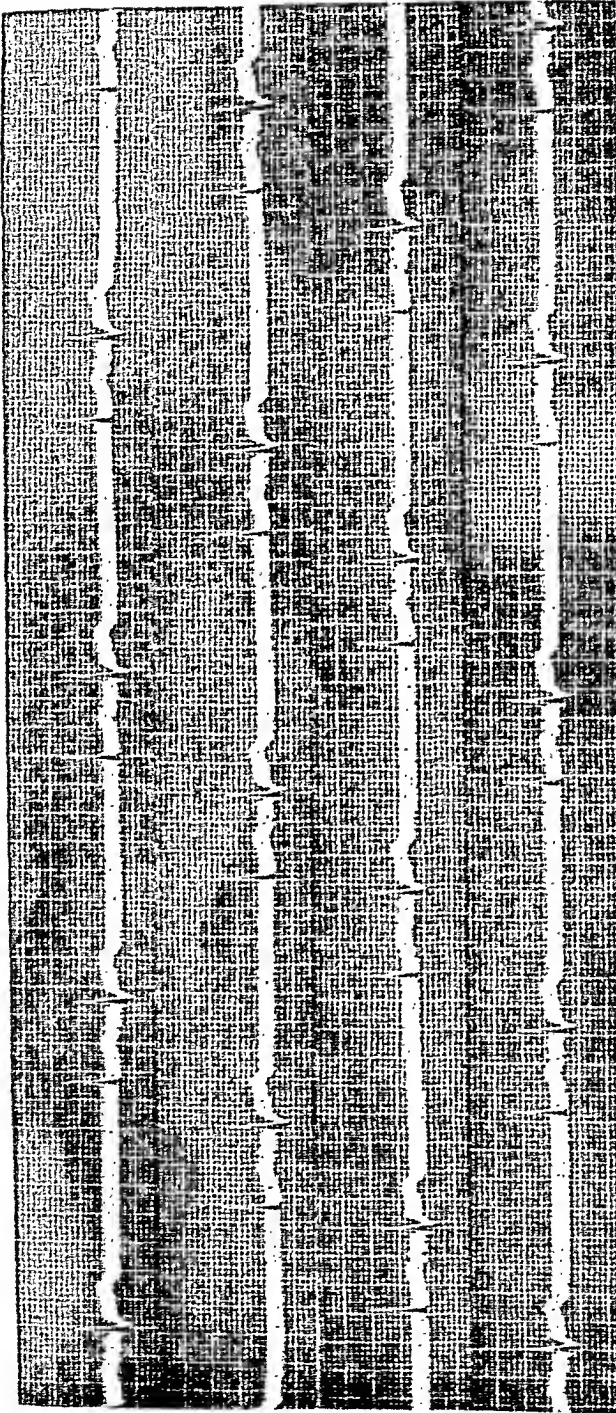


Fig. 3B.—Continuous tracing of portion of Lead II. R-R intervals as follows: R₁-R₂, 0.57; R₂-R₃, 1.74; R₃-R₄, 0.57; R₄-R₅, 1.70; R₅-R₆, 0.57; R₆-R₇, 1.74; R₇-R₈, 0.57; R₈-R₉, 1.71; R₉-R₁₀, 0.57; R₁₀-R₁₁, 1.75; R₁₁-R₁₂, 0.57; R₁₂-R₁₃, 1.75; R₁₃-R₁₄, 0.57; R₁₄-R₁₅, 1.80; R₁₅-R₁₆, 0.57; R₁₆-R₁₇, 1.78; R₁₇-R₁₈, 0.57; R₁₈-R₁₉, 1.73; R₁₉-R₂₀, 0.57; R₂₀-R₂₁, 1.77; R₂₁-R₂₂, 0.57; R₂₂-R₂₃, 1.72; R₂₃-R₂₄, 0.57; R₂₄-R₂₅, 1.72; R₂₅-R₂₆, 0.57; R₂₆-R₂₇, 1.71; R₂₇-R₂₈, 0.57; R₂₈-R₂₉, 1.66; R₂₉-R₃₀, 0.57; R₃₀-R₃₁, 1.74; R₃₁-R₃₂, 0.57; R₃₂-R₃₃, 1.76; R₃₃-R₃₄, 0.57; R₃₄-R₃₅, 1.72; R₃₅-R₃₆, 0.57.

R-R interval between the first and second beats was fixed at 0.53 second; the interval between the second and third beats varied from 0.52 to 0.62 second. The interval between the dominant A-V beats was 2.00 to 2.04 seconds. Three minutes later the rhythm was again bigeminal in character. The rate of the dominant rhythm had become accelerated, and the R-R interval was 1.50 seconds, while the coupling time had decreased to 0.50 second. Five minutes later, the

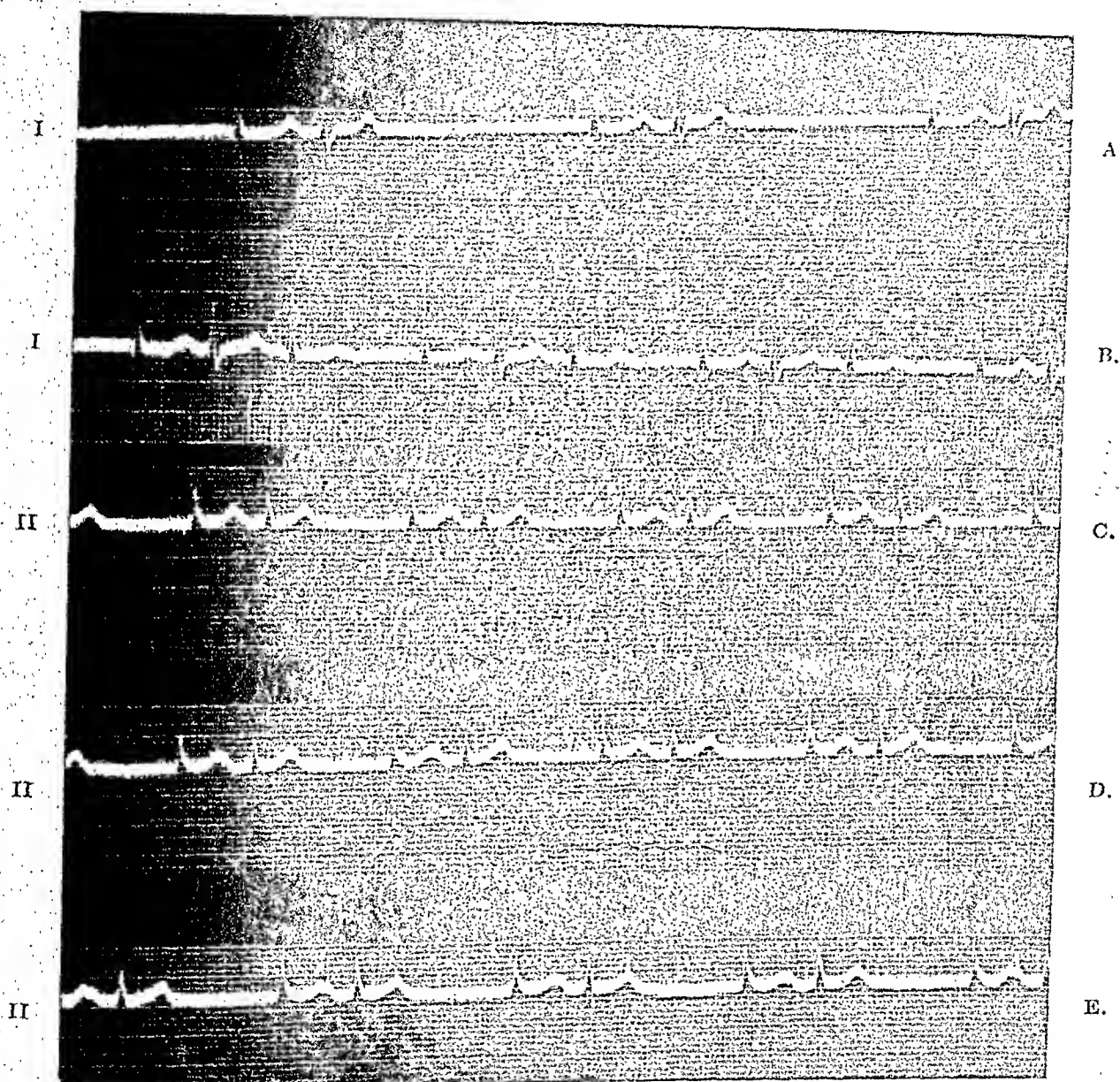


Fig. 4.—Aug. 27, 1945. A, Control record. B, One minute after intravenous atropine sulfate. C, Three minutes later. D, Five minutes later. E, Thirty minutes later.

dominant A-V rhythm presented a cycle length of 1.48 second and the coupling interval was still 0.50 second. At the end of thirty minutes the dominant rhythm had slowed, with a cycle length of 1.64 seconds, and the couplet interval had increased to 0.52 second.

In Fig. 5 are shown A-V nodal beats which were preceded in Lead II by inverted P waves. We interpret this to show that retrograde conduction could

occur normally under certain circumstances. The A-V nodal beats which were preceded by retrograde P waves invariably occurred at an interval after the preceding beat which was shorter than the usual interval between nodal beats in this case. This suggests that facilitation of retrograde conduction took place when one nodal beat followed another at a comparatively short interval.

A triple rhythm was seen under the following circumstances: after stimulation of the right carotid sinus, after the administration of atropine sulfate, and also on one occasion as a spontaneous phenomenon.

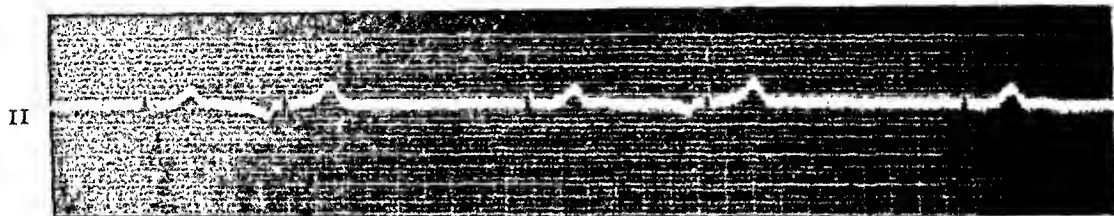


Fig. 5.—Aug. 21, 1945.

Comment.—Analysis of the electrocardiograms yielded the following pertinent data:

1. An unusual and remarkably persistent type of atrionodal rhythm with ventricular bigeminy was present. In all, 270 couplets were recorded, and the longest consecutive run consisted of seventy-one pairs.
2. Between the bigeminal ventricular beats an antegrade but aberrant auricular complex was present.
3. Rarely the first beat of the couplet was an idioventricular escape beat.
4. On some occasions, the second ventricular beat was aberrant, due to functional right bundle branch block.
5. The coupling was consistently fixed on any given day, although it varied slightly from day to day. The interval varied from 0.57 to 0.72 second when the dominant rhythm was atrionodal in origin, and from 0.76 to 0.80 second when idioventricular beats were dominant.
6. Despite slight, or even marked variations in the interval between dominant atrionodal beats, the coupling of the second beat to the first remained fixed.
7. Two exceptions to this rule occurred in Fig. 2, in which one couplet was shorter and one longer than the other pairs present on this occasion.
8. The rate of the dominant rhythm was unusually slow at times and was as low as 18 per minute.
9. The bigeminy was not influenced by change of posture, exercise, respirations, oculobulbar or carotid sinus pressure, or nitroglycerine.
10. After administration of atropine sulfate intravenously, the rate of the dominant rhythm was accelerated. However, the pairing was not interrupted, although the cycle length of the bigeminy was shortened.
11. A triple rhythm occurred spontaneously, after pressure on the carotid sinus, or one minute after the intravenous administration of atropine. The

last beat of each triplet was probably of abnormal auricular origin and was not coupled to the preceding beat at a fixed interval.

12. The bigeminy never occurred without the presence of the intervening abnormal auricular beat and the latter never appeared independently, or without being followed by a ventricular response.

DISCUSSION

We could discover in the literature only three cases of atrionodal rhythm with ventricular bigeminy and an intervening antegrade P wave. Gallavardin, Dufourt, and Petzetakis¹² reported the first one in 1914. They believed two independent rhythms, one atrionodal, the other sinoauricular, were present. This was clearly an instance of interference dissociation. White¹⁴ described a case of reciprocal rhythm in 1921 in which on one occasion the P wave between ventricular beats was upright. As an explanation of this phenomenon, he suggested that the mechanical theory might apply to reciprocal rhythm, that the abnormal auricular beats were excited by the contractions of the ventricles and were in turn followed by ventricular responses. Herve and Besoain (1942)¹⁰ described a case in which, preceding the onset of the bigeminal rhythm, the pacemaker in the sinus node shifted to a lower center. A pause then ensued and the atrioventricular node escaped. This escape beat was followed in turn by a supra-ventricular beat in which the P wave was identical with the last one before the pause and, therefore, originated in an abnormal location in the sinoauricular node. A run of bigeminy, consisting of paired nodal escape and abnormal sinoauricular beats, then occurred. The authors did not attempt to explain the mechanism of this arrhythmia. The tracings in their publication were so reduced in size that accurate measurement was impossible, and we do not know whether or not the coupling was fixed.

Our case resembled superficially those described in the foregoing. However, the mode of onset and termination of the bigeminy differed from the transitions which occur in interference dissociation, and we were unable to demonstrate a shifting pacemaker prior to the onset of the bigeminy. The bigeminy was more persistent than in any previously reported cases and allowed more detailed observations to be made.

The first explanation of the mechanism which suggests itself is that the bigeminy may be due to the fortuitous pairing of two independent rhythms. To rule out this possibility the following facts are offered:

1. The rhythm was unusually persistent. It is conceded that in some instances of A-V interference dissociation there may be short intervals during which the rates of the two rhythms are identical, or nearly so. However, the sinus rhythm sooner or later is accelerated, and when it exceeds the rate of the A-V node, it resumes command of the entire heart. The bigeminy in our case did not terminate in this manner.

2. The abnormal P wave never appeared independently but always followed a preceding atrionodal beat. If the two rhythms were unrelated, we would expect the second to precede the first at some time.

3. The coupling was fixed for long periods of time despite slight to marked variations in rate of the dominant rhythm. On one occasion the fixed coupling was maintained throughout a sequence of seventy-one pairs of beats.

4. The coupling was not interrupted by exercise, change of posture, forced breathing, oculobulbar or carotid sinus pressure, nitroglycerine, or intravenous atropine sulfate. If there were two independent rhythms present, it is reasonable to anticipate that they would react in different degree to the foregoing stimuli.

5. The rate was too slow both for an independent A-V rhythm and a nomotopic or ectopic auricular rhythm.¹⁵

It is, therefore, probably safe to conclude that the coincidence of the two rhythms was not fortuitous but that the second one was linked in some way with the first. It may further be assumed that the abnormal auricular beat was excited by the preceding ventricular contraction and was, in turn, followed by a ventricular response. Determination of the origin and mechanism of the P wave in question holds the key to the solution of this case. Study of the P waves reveals the following: They were abnormal for this case. They were obscured to some extent by the fact that they fell on the descending limb of the preceding T wave, but they could be seen to differ definitely in contour from obviously normal S-A complexes. The P waves presented an antegrade pattern. They were upright in Leads I and II and inverted in Lead III. How then can the dependence of an abnormal antegrade P wave on a preceding ventricular beat be explained?

Two possibilities are presented for consideration. Either the two beats are connected electrically or the coupling is due to some other mechanism.

If there is electrical continuity between the first ventricular beat and the P wave which follows, can this case be one of reciprocal rhythm? And if it is reciprocal rhythm, how can the absence of a retrograde P-wave pattern be explained? As a corollary to the last question, it may be asked, can a stimulus which originates in the A-V node, and secondarily excites the auricle, cause an antegrade P-wave pattern? From the electrical standpoint this would appear impossible, certainly if there were present a normal pathway for retrograde conduction. However, from time to time the statement appears in the literature that an A-V nodal beat might give rise to an upright P wave in Lead II. Gallavardin and Gravier¹⁶ proposed that variations in the form and position of the P wave depend upon the portion of the auricle upon which the impulse from the A-V node impinges first. They pointed out that the stimulus from the A-V node need not fall first upon the lower part of the auricle but that it may reach its upper portion first because of distribution of conducting tissue in the auricles. Chamberlain¹⁷ endorsed this concept. McQuire and Rosenberger¹⁸ and Edens¹⁹ also agreed that nodal P waves need not be inverted. Lewis²⁰ stated that the P wave in A-V nodal rhythm is inconstant in form but usually inverted. Experimentally, Scherf and Shookhoff^{21,22} and Rothberger and Scherf²³ showed that the P waves in nodal rhythm may be upright but abnormal in form. Katz²⁴ designated as coronary nodal rhythm those cases in which upright P waves precede QRS responses by a short interval and suggested that the P waves originated

in the upper strands of the A-V node which lie in the auricle near the sinus node. Langendorf, Simon, and Katz²⁵ suggested that there may be present intra-auricular block which makes the path resemble that taken by sinus beats.

Although there may be some reasonable difference of opinion on this point, the majority of present-day investigators agree that an A-V nodal impulse cannot give rise to an antegrade P wave. Moreover, in the case which we have presented there is evidence that retrograde conduction could take place, for occasionally an inverted P₂ did precede a ventricular response. If reciprocal rhythm were present, we might expect to find an inverted P₂ between the ventricular contractions.

Consideration must be given next to the possibility that although this case is not one of reciprocal rhythm, nevertheless there is electrical continuity between the two beats; that is, the auricular beats may be extrasystoles coupled with a dominant A-V nodal rhythm. Since the coupling was fixed, it might be argued that the extrasystoles were due to re-entry. However, in order to have re-entry, it is first necessary to demonstrate entry. There is a remote possibility that retrograde conduction to the auricle did accompany the first ventricular beat but that the auricular component in the electrocardiogram was buried in the QRS complex. The next auricular beat might then be coupled as a re-entrant phenomenon with this retrograde auricular impulse. However, the evidence in our case tends to negate this hypothesis. Coupling occurred after idioventricular beats as well as after atrionodal beats. Retrograde conduction following ventricular beats is, in itself, a rarity. Usually the R-P interval is somewhat longer than that following A-V nodal beats and the P wave can be seen superimposed on the S-T segment or T wave. We found no evidence of retrograde conduction with idioventricular beats in our case. This theory would not explain the response to intravenous atropine, in which the coupling interval was decreased. This response would necessitate the assumption that the re-entrant pathway had become shortened following diminished vagal tonicity. Furthermore, exercise, which might be expected to cause disappearance of extrasystoles, was without influence upon the bigeminy.

Since we cannot demonstrate electrical connection between the two beats, we must turn to consideration of another mechanism by means of which one beat might provoke another, the so-called mechanical theory. This theory was first invoked by Cohn and Fraser²⁶ to explain premature auricular contractions which occurred at a short interval after ventricular systole in complete heart block. Wilson and Robinson²⁷ suggested that the same effect of ventricular systole upon the normal sinus pacemaker might account for the peculiar sinus arrhythmia encountered in complete heart block. Barker²⁸ demonstrated in animal experiments that a sudden increase in intraventricular pressure would initiate a premature ectopic auricular beat. He assumed that the ventricular contraction mechanically stimulated a focus in the bundle above the supposed lesion and provoked a premature beat which was conducted through the auricles by the normal path. White¹⁴ offered the mechanical theory as an alternate explanation for one of his cases of reciprocal rhythm. Wolferth and McMillan,²⁹

however, objected to this theory and pointed out that the R-I' interval in reported cases was too short to accommodate Barker's double mechanism. They presented an analysis of three cases of ventriculoauricular sequential beats with relatively short R-P' intervals and concluded that this arrhythmia was best explained on the basis of retrograde conduction. Moreover, they were unable to prove mechanical stimulation of the auricle by ventricular systole in animal experiments. Later observers have been unanimous in rejecting the theory of mechanical stimulation (Winternitz and Langendorf,³⁰ Parkinson,³¹ Parsonnet and Miller,³² Scherf,³³ and Kisch and Zucker³⁴). Thus, although cardiac muscle tissue, in common with other types of muscle tissue, does respond to direct mechanical stimulation, there is no experimental or electrocardiographic evidence that contraction of the ventricle in itself constitutes a proper stimulus to cause an auricular systole.

None of the foregoing theories is adequate to explain the mechanism in our case, nor can we offer a more plausible one. Any acceptable theory must account for the unusual persistence of the bigeminy, the lack of response to the sinus reactions, the coupling with idioventricular beats, the response to atropine, the rare exceptions to the rule of fixed coupling, the presence of triplets, and the unusually slow dominant rhythm. We are led to the conclusion that this is another example of the fact that one beat may in some unknown way stimulate a second one. If the trigger mechanism by which this stimulation occurs were known, many perplexing problems in electrocardiography might be clarified.

SUMMARY

1. A case of atrionodal rhythm with ventricular bigeminy of unusual mechanism is presented.

2. The sequence of events was probably as follows: Periodically there occurred marked depression of the sinus nodal pacemaker accompanied by depression of the lower automatic centers as well. As a result, sinus pauses occurred, with either the A-V node or the ventricle taking command of the heart, either as a series of escape beats or as a dominant atrionodal or idioventricular rhythm. The dominant beats were followed at a fixed interval by abnormal auricular complexes which originated either in the S-A node, outside of the normal pacemaker, or in the auricle. The auricular beats were followed in turn by ventricular responses which were normal or aberrant in contour. Apparently the second ventricular systole led to further depression of the dominant pacemaker so that the rate was unusually slow.

3. The possible mechanisms which might account for this unusual bigeminy were reviewed but none was found applicable to this case.

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A NEW SENSITIVE PORTABLE PLETHYSMOGRAPH

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FOR several years studies have been conducted on peripheral blood vessels at Tulane Medical School and the Rockefeller Institute for Medical Research with the use of a sensitive plethysmograph. The apparatus went through various stages of development from time to time as each new unit was constructed. In most instances the units were not portable and in many ways rather difficult to use. It was not possible, for example, to obtain linear variations in the plethysmogram in standard units without a process of fairly lengthy calculations to correct for size of the part and sensitivity of the recorder. The sensitive recording capsules were made of a thin rubber membrane which disintegrated very rapidly, resulted in difficulties with leaks, and necessitated constant service. Because of these and many other difficulties it was decided to build a sturdy, portable, and practical plethysmograph for clinical and experimental purposes which would require no constant servicing and which would record a plethysmogram that could be standardized and read easily and directly just as one reads an electrocardiogram. It, therefore, is the purpose of this paper to describe the model of a sensitive portable plethysmograph developed in our laboratory, to indicate in detail the use of the one now available,* and to point out some of the fundamental aspects of recording, interpreting, and applying the plethysmogram to physiologic and clinical problems. It is not the purpose of this discussion to review the development of plethysmography nor to review the physiologic or clinical applications of plethysmography in detail.

THE PLETHYSMOGRAPH

The model of the plethysmograph constructed in our laboratory is shown in Figs. 1 to 4. It consists of (1) a sensitive volume-recording metal bellows or capsule which activates a mounted bow and bowstring, (2) lighting and lens systems for focusing the bowstring, (3) a coarse volume recording system, (4) timers, (5) a camera, and (6) a selector valve. These parts are shown in Figs. 1 to 4.

The principle and mechanics of the apparatus are very simple. A diagrammatic representation of the apparatus is shown in Fig. 1. The pneumatic system

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*The plethysmograph that will be described is now made by the Cambridge Instrument Company of New York, New York, N. Y.

consists of the sensitive metal capsule (d' , Fig. 1, *B*, and Fig. 3), a metal bellows (p , Fig. 1, *C*, and Fig. 4) to control the position of the bowstring, and an extremity cup (Fig. 5, *C*). These three units are connected together at atmospheric pressure by means of a thick-walled and narrow bore (1 mm.) rubber tubing. Once the pneumatic system is closed, any change in volume of the part enclosed in the extremity cup produces a change in volume of the sensitive metal capsule (d' , Fig. 1, *B*, and Fig. 3). When this sensitive metal capsule moves, it activates

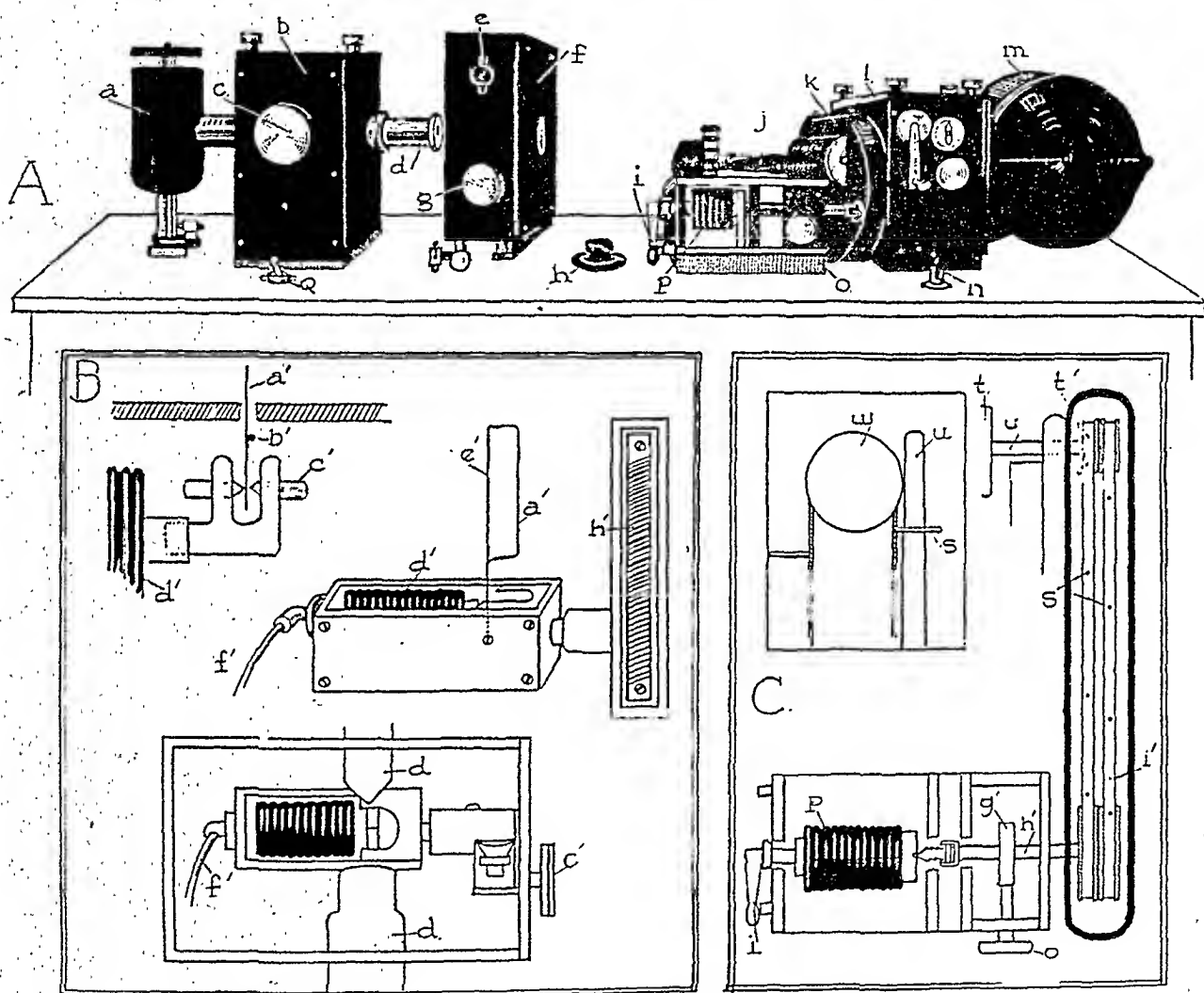


Fig. 1.—Diagram of the plethysmograph developed in our laboratory. The details are described in the text. This plethysmograph served as the model for the instrument that is now available commercially (Fig. 6).

a very short arm of a light aluminium tube (weight, less than 30 mg.), shaped essentially as a question mark (?), about a pin or axis set preferably in jewel bearings. The relatively very long or bow-shaped end (a' , Fig. 1, *B*) moves a great deal (mechanical magnification, 40 \times). On this bowstring is stretched a fine tungsten string (e' , Fig. 1, *B*) which is enlarged about 150 times and focused by satisfactory lenses (d) onto the moving photographic paper of an ordinary type electrocardiograph camera. Satisfactory arrangements are made so that photographing can be done in a room with ordinary amounts of lighting. The

selector valve (*h*, Fig. 1, *A*) is connected to three rubber tubes which in turn may be connected alternately to three extremity cups or parts. Also connected to the pneumatic system is another bellows, a coarse recorder bellows or baseline adjustment bellows (*p*, Fig. 1, *A*). The volume within this bellows can be varied by turning the knob, (*o*, Fig. 1, *A*). When this knob is turned, the shaft, to

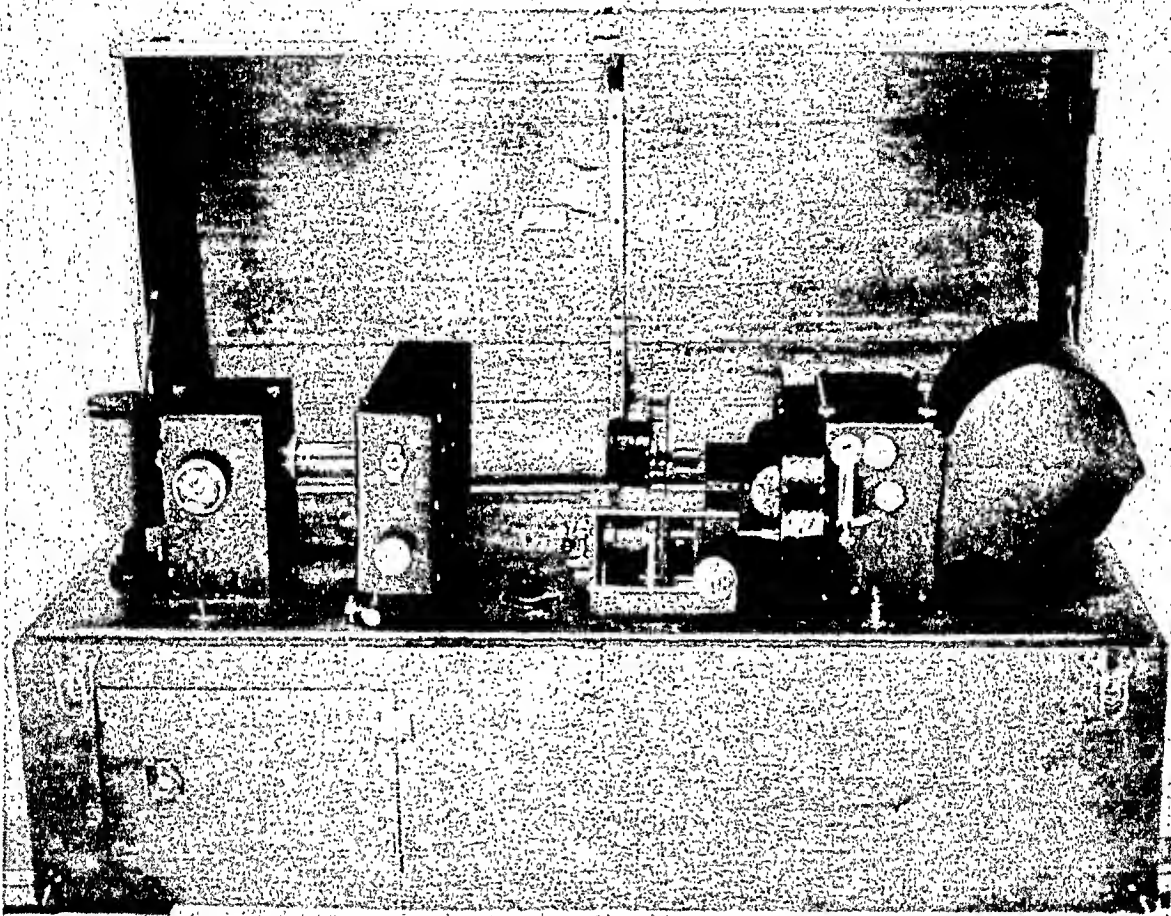


Fig. 2.—Photograph of the plethysmograph constructed and used in the laboratory. From left to right are seen (1) the lamp, (2) the housing and lens system for the sensitive recording bellows, bow, and bowstring, (3) the timer housing and lever for making the necessary changes for slow and speed recording, (4) the selector valve, (5) the calibrator level, (6) the baseline recorder, (7) the interval elapsed timer recording pins and baseline recorder pins, and (9) the camera. The exposed photographic paper receiver is located under the camera.

which are attached a screw on one end and a pulley on the end near the camera, is rotated. Any change in volume of the baseline adjustment bellows produces a shift in the sensitive metal capsule, thus moving the bow and bowstring. At the same time the pulley attached to the other end of the shaft rotates and moves a metal tape (*i*' Fig. 1, *C*) on which are attached metal pins (*s*, Fig. 1, *C*) which cast shadows on the photographic paper. The pins are so spaced that one

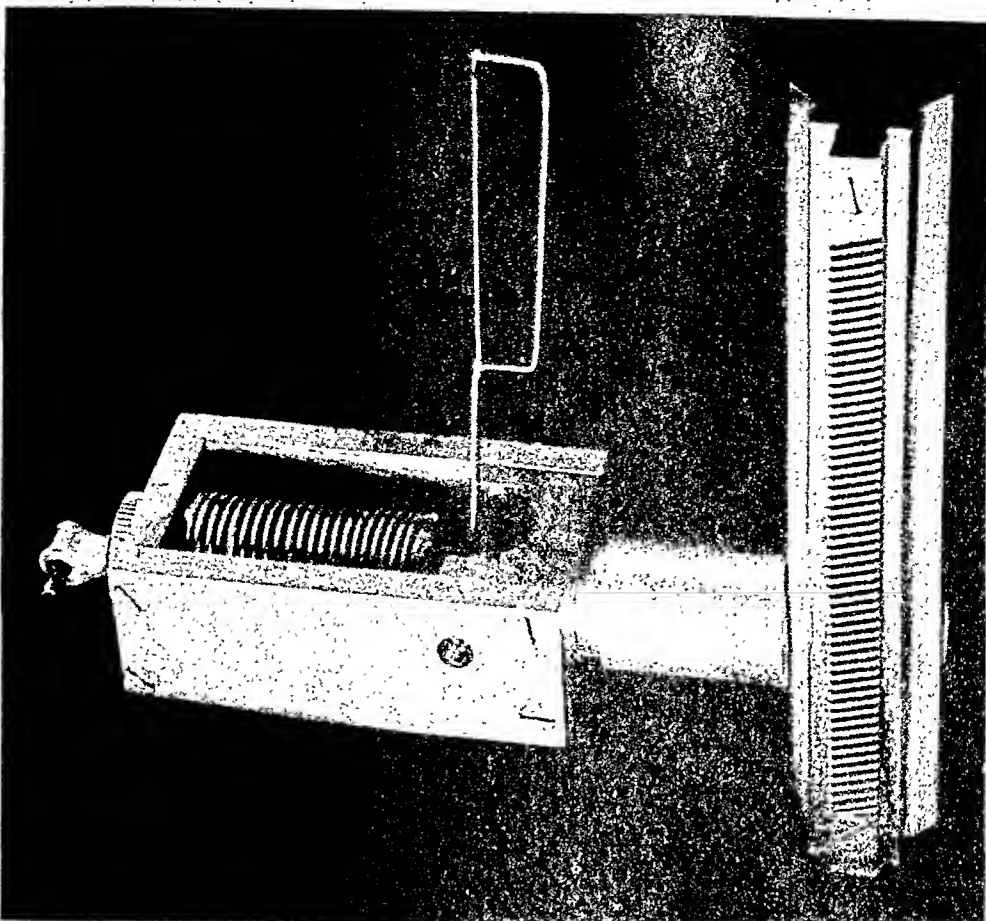


Fig. 3.—Photograph of the sensitive bellows, bow, and bowstring assembly mounted on a rack. The bowstring rotates around the watch type of steel bearing. The bellows was changed later to a dome-shaped aluminum membrane which activates the bow and bowstring in a similar fashion.

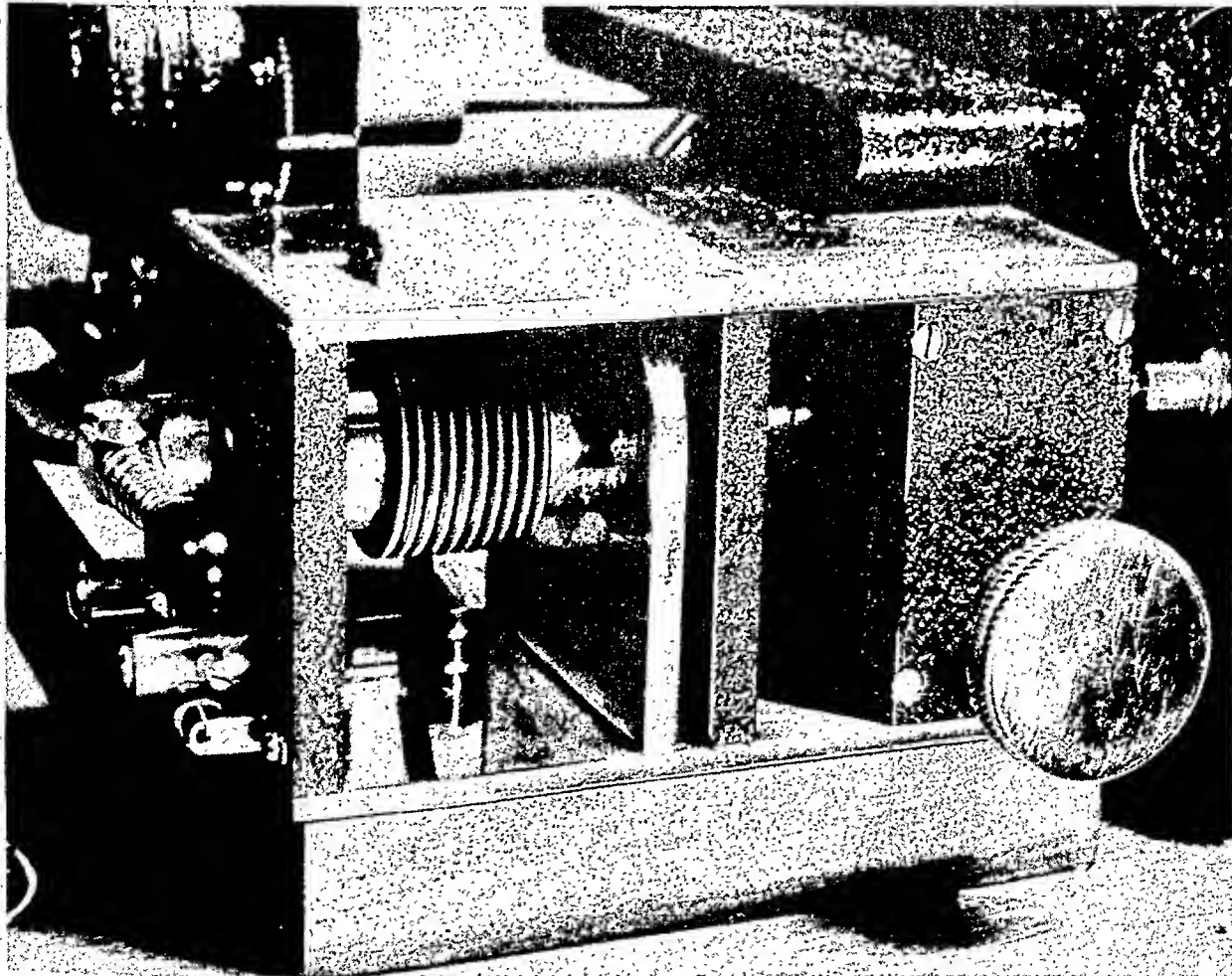


Fig. 4.—A photograph of the calibrator lever, baseline adjustment bellows, and knob which controls a worm and gear. Consult the text and Fig. 7 for the details.

is always casting a shadow on the photographic paper. A movement of the pin shadows of 1.0 mm. represents 1 c.mm. volume change in the pneumatic system.

On the other end of the housing of the baseline adjustment bellows is another screw fixed to a calibration lever (*i*, Fig. 1, C). By means of stops adjusted by set screws, a partial rotation of the *calibration lever* (*i*, Fig. 1, C) effects a 10 c.mm. change in volume within the pneumatic system. This change in volume results in a movement of the bowstring, thus making it possible to convert linear change

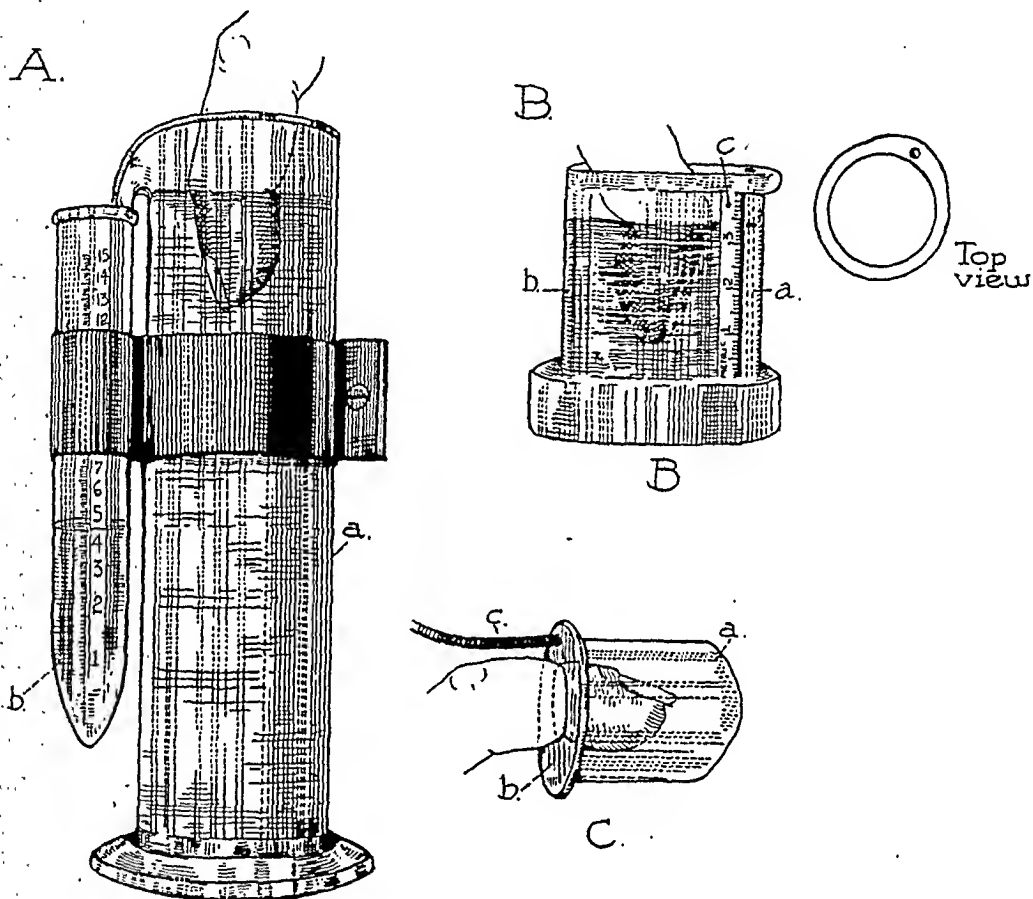


Fig. 5.—Drawing of the apparatus, A and B, used to measure the volume of that part for study. In A, the volume of water displaced by the part spills from the cylinder, *a*, to the graduated test tube, *b*, for measurement. In B, the volume of water displaced by the part displaces a meniscus in the narrow bore tube, *a*, which connects with cylinder, *b*, near the base. Consult the text for details and other methods. C shows an extremity cup in place.

in the bowstring shadow of the completed plethysmogram to cubic millimeter change in volume of the part enclosed by the extremity cup. Since the parts of the extremity (finger and toe tips) vary in size, it is necessary to adjust the sensitivity of the bowstring in order to reduce all linear movements of the string shadow to a standard unit of volume of a standard-sized part. The sensitivity of the bowstring is varied by means of the sensitivity adjustment knob (*c*, Fig. 1, A) which rotates a pinion and lifts or lowers the sensitive metal capsule, bow, and bowstring which are mounted on a rack. This makes it possible to focus

a small segment of the bowstring near the fulcrum of the bow or a segment farther away. Thus, by varying the length of the lever, it is possible to select, within desired limits, a relatively large or relatively small amount of movement of the string shadow for a given change in volume within the pneumatic system (see paragraph on Standardization of the String).

During the course of recording, it is sometimes advisable to discontinue the actual recording in order to save photographic paper and to avoid the accumulation of a cumbersome record; at the same time, the interval of time that elapses when the camera is off is often important to know and record. This is done automatically by a *master timer* or *elapsed time indicator*, synchronous timer (*t*, Fig. 1, C) which rotates a pulley and metal tape (*t'*, Fig. 1, C). Fixed to the tape are four pins of different diameters which cast shadows of different widths on the completed plethysmogram. A movement of a timer pin shadow of 4 mm. is equivalent to the elapse of one minute in time. From the width of the timer pin shadows and their relative positions before stopping the recording and at the beginning of the next interval of recording, the duration in time that the camera was off is measurable to a fraction of a minute. This feature is of value when the effects of stimuli, drugs, and other agents are being studied.

The plethysmograph made available commercially is shown in Figs. 6 and 7. The detail descriptions of the unit are indicated in the legends. All future references and discussions will be concerned with this unit.

Horizontal millimeter lines and time lines are produced on the plethysmogram in a manner similar to that in the electrocardiograph. One timer produces a vertical mark every 0.04 second in the same fashion used in electrocardiography and the other, a shadow every 15 seconds. By means of a speed control knob or lever (Figs. 1 and 6, 22) a simple rotation of the lever results in a change in the speed of the camera with a movement of the recording paper from a rate of 9.5 cm. a minute (slow speed) to about 145 cm. per minute (fast speed) and vice versa. By means of suitable levers and switches the light intensity, the timers, and the camera speed are changed with each simple rotation of the *speed control lever* (Fig. 6, 22). This ensures a good recording at the two speeds.

The extremity cup (Fig. 5, C) is made of thin-walled transparent plastic test tubes. One end is closed with a diaphragm made of the same material. The diaphragm has a hole shaped to fit the finger or toe tip loosely. Entering the cup through the diaphragm is a thin-walled brass tube to which is connected the rubber tubing from the plethysmograph. A fairly large assortment of cups should be available in order to make possible a fit for a finger or toe of any size. The cups are chosen to ensure a minimum dead space without the part resting against the wall. The finger or toe tips are inserted into the hole of the diaphragm until the edges of the hole reach the distal major dorsal and ventral skin creases at the distal interphalangeal articulation. A seal between the cup and the part is made with warm printers' roller compound brought to the proper consistency and stickiness with LePage's glue.

Physical Characteristics of the Sensitive Metal Capsule.—The crucial portion of the instrument from the physical point of view is the sensitive metal capsule

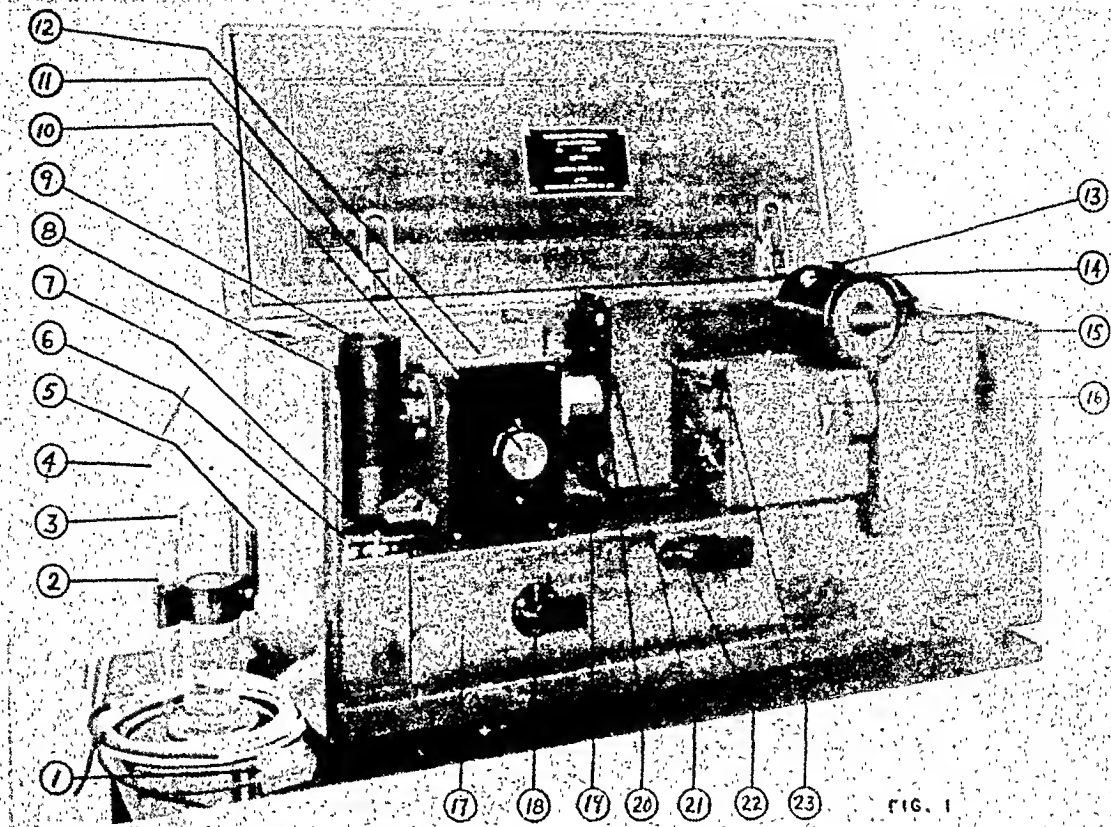


FIG. 1

Fig. 6.—The plethysmograph commercially available. The labelled parts are 1, extremity cup; 2, calibrated test tube; 3, measuring cylinder; 4, rubber tubing leading from extremity cup to the plethysmograph; 5, socket for power supply; 6, light and slow timer switch; 7, camera and fast timer switch; 8, condenser lens; 9, lamp; 10, storage compartment; 11, sensitivity adjustment knob; 12, inspection plate; 13, exposed photographic paper receiver; 14, lever for opening and closing receiver and cutting the photographic paper; 15, latch for leading the camera; 16, knob for controlling baseline adjustment; 17, inspection panel; 18, selector valve; 19, focusing screw; 20, fast timer; 21, slow timer; 22, speed control lever; and 23, calibrator lever.

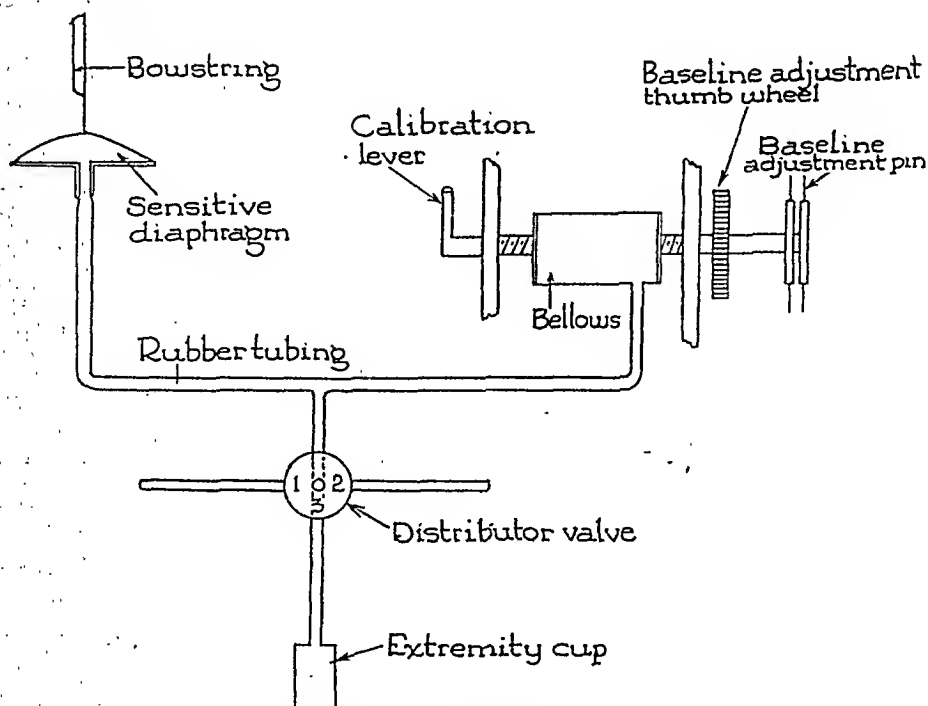


Fig. 7.—Diagram of the pneumatic system and recording parts of the plethysmograph shown in Fig. 6. Consult the text for details.

or diaphragm (0.002 inch thick aluminum) which is designed to give a true record of relatively rapid changes in volume. As pointed out by Wiggers,¹ in his discussion of the recording of pressure pulses, the vibrating membrane must have certain characteristics in order for it to reproduce accurate records of the physical phenomena to be measured.

Natural Frequency.—The natural frequency of the sensitive metal capsule is about 150 cycles per second. This more than meets the necessary requirements and also makes the instrument quite suitable for the study of animals with very rapid pulse rates, such as is encountered in the rat or in the upstroke of the pulse waves, or the dicrotic notch.

Damping.—Fig. 8 shows the string shadow of the sensitive metal capsule to be damped properly, thus avoiding errors due to overshooting or overdamping.

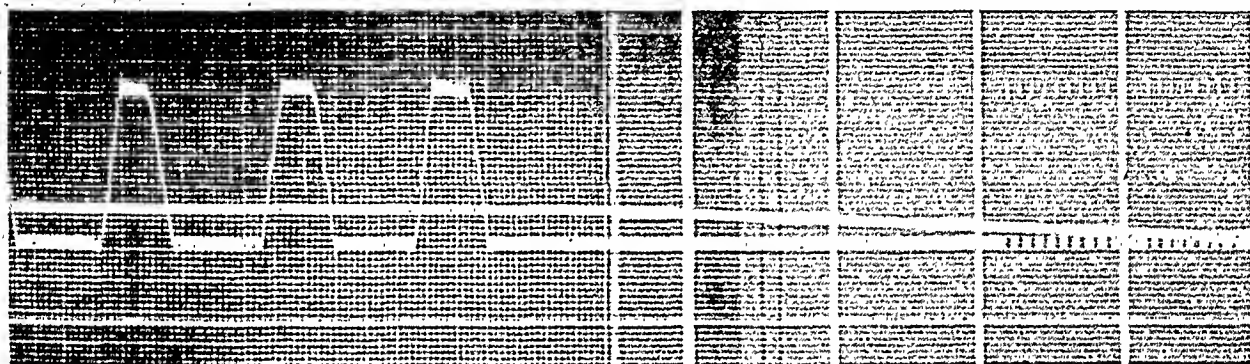


Fig. 8.—Tracing showing the adequate damping of the bowstring. A shift of the bowstring shadow represents 10 c.mm. change in volume within the system. The first portion was recorded at fast speed (standard camera speed employed in electrocardiography) and the second portion was recorded at slow speed. The time interval represented by the distance between each broad vertical white line in the slow speed recording is fifteen seconds.

Relation of Rate of Vibrations to Linear Deflection of the Bowstring.—A mechanical device in which alternate compression and release of a metal bellows produced a constant change in volume at desired rates, from very low frequencies to very high frequencies, was connected to the pneumatic system of the plethysmograph. Fig. 9 shows the results of these studies. The string shadow recorded the true volume change at complete cycle frequencies as high as are encountered in the study of human and other animal subjects. This (Fig. 9) indicates the suitability of the apparatus for the study of animals with very high cardiac or pulse rates after suitable correction.

Influence of Pressure in the Pneumatic System.—The relationship of volume change within the pneumatic system to deflection of the string shadow within the range of the working pressure (2 to 24 mm. of water) is shown in Fig. 10. Since this is a volume recorder, the fact that the linear movement of the string shadow does not vary for a given volume change within the pneumatic system within the variations in pressure used during recordings indicates an excellent physical feature of the sensitive aluminum capsule.

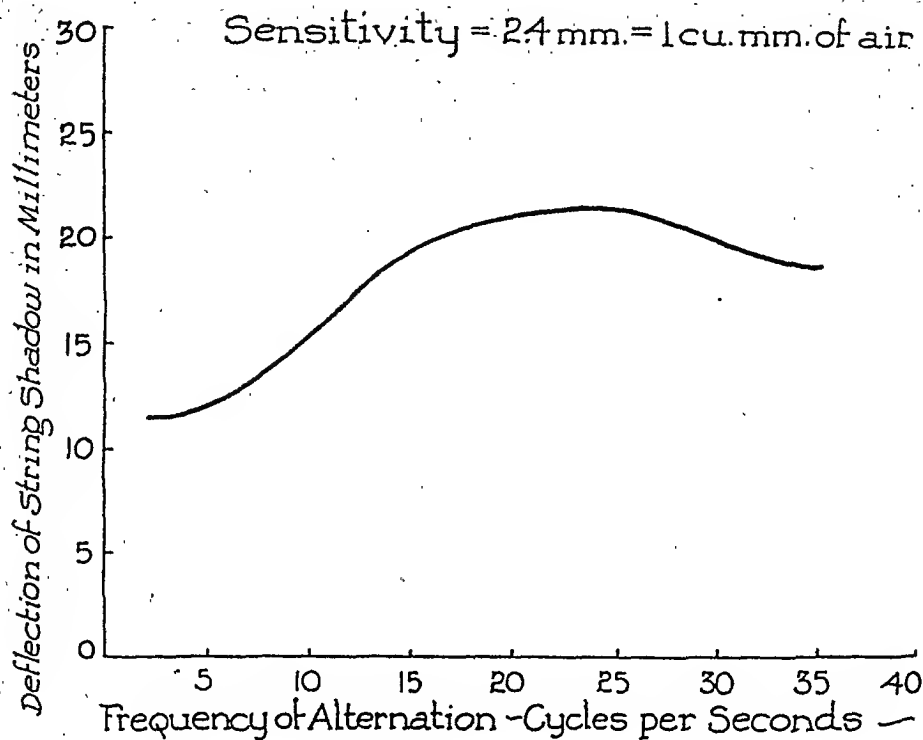


Fig. 9.—Frequency response curve of an aluminum diaphragm activated by air from a bellows being alternately compressed and released. Curve shows the variations in sensitivity of the bowstring of the plethysmograph with variations in rate of its movement. The upstroke of the pulse wave at resting heart rates has a frequency about five cycles per second.

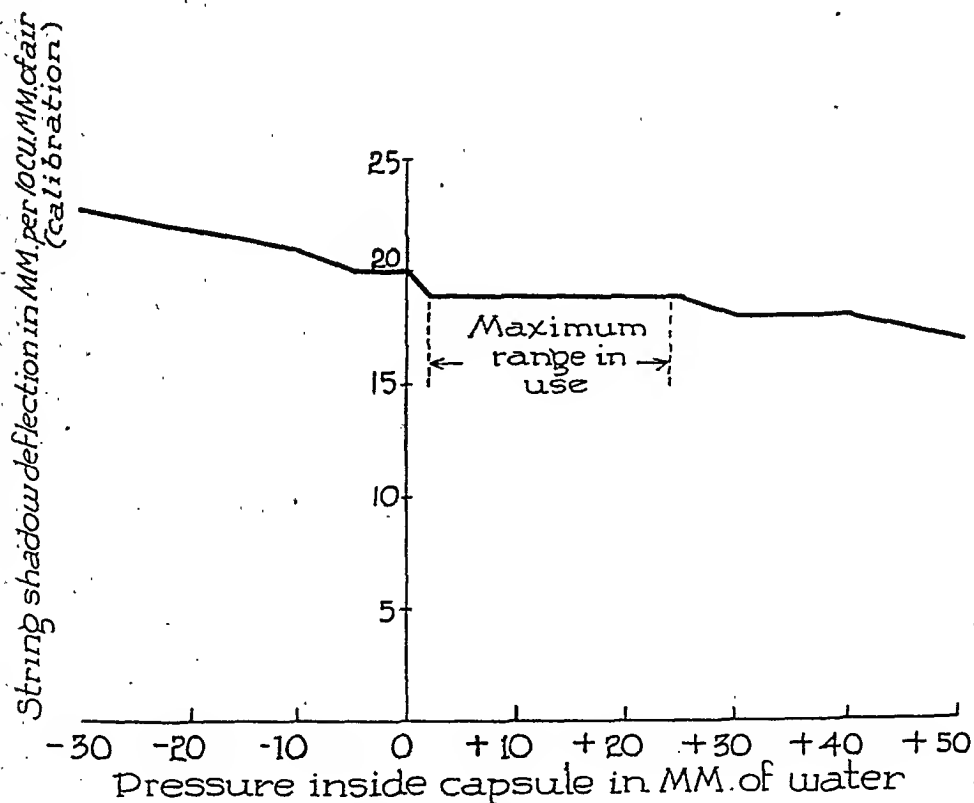


Fig. 10.—Response of .002 inch aluminum diaphragm to a standard 10 c.mm. calibration, with changing internal pressure. Variations in sensitivity of the bowstring with variations in the pressure within the closed pneumatic system. Within the pressure range of use the sensitivity of the bowstring does not vary.

METHOD OF RECORDING THE PLETHYSMOGRAM

The conditions and method for recording the plethysmogram described are intended for relatively ideal conditions of study. It is obvious that such conditions are not always available. Good work can be performed under less satisfactory conditions, but it is necessary that the standards for the normal and the method be established for the working conditions. Any comparisons with the results of others must be interpreted in the light of the circumstances of study. Once an observer becomes acquainted with his conditions of study, he will have no difficulty in applying plethysmographic methods to his patients.

The Observation Room.—When studying patients for physiologic phenomena concerned with the peripheral blood vessels of the tips of the fingers and toes, it is best to have a proper type of observation room.² The atmosphere of the room should be comfortable. It has been found that a temperature of about 23.8°C. (75°F.) and a relative humidity of about 50 to 60 per cent are good atmospheric conditions for a resting subject. It is also advantageous to have an air-conditioning unit which can make possible a dry or wet cold atmosphere and a dry or wet warm or hot atmosphere. This makes it possible to study the ability of the circulation to react to stimuli that produce vasoconstriction and vasodilation, reactions of great value in differentiating organic and functional occlusive vascular diseases. The room should be free of drafts of air; that is, the rate of movement of the room air should be less than fifteen feet per minute. The room should be made cozy, comfortable, and free from any intricate apparatus. This leads to relaxation on the part of the patient and reduces anxiety and other psychic phenomena to a low level. The patient should rest on a comfortable bed with the part that is to be studied held at heart level.

Clothing.—The patient should remove all clothing or at least everything except loose-fitting underwear. Covering with a sheet or blanket may be permitted. It is necessary to be careful not to allow him to become cool or warm; he must be comfortable. A patient who enters an air-conditioned room at 75°F. may want to cover because of chilliness, but he is likely to warm up and become too warm if great care is not observed. The best rule to follow is to have the patient comfortable.

Position of the Part for Study.—The part for study should rest at the level of the heart. To ensure a proper position for the finger tips, an adjustable and comfortable armrest is preferable (Fig. 11). Pillows may be used if a special armrest is not available. It is *imperative* that the extremity cup does not touch anything. It is necessary that the arm be adjusted in a position that is comfortable for the patient and free from any torsion on the blood vessels. It has been found that a slight abduction of the arm at the shoulder with a slight flexion of the forearm at the elbow and with the hand in the "handshake" position with complete relaxation of the muscles of the entire extremity is the best position for study of the finger tips.

Special Preparation of Patient.—No special preparation of the patients is required for the studies. It is better that they refrain from smoking and the use of alcohol or drugs for a time sufficiently long to ensure that these agents will not influence the blood vessels. The same is true for food or fluids. Essentially the same precautions should be employed that are generally accepted for recording the electrocardiogram. Special periods of fasting and basal conditions are not necessary.

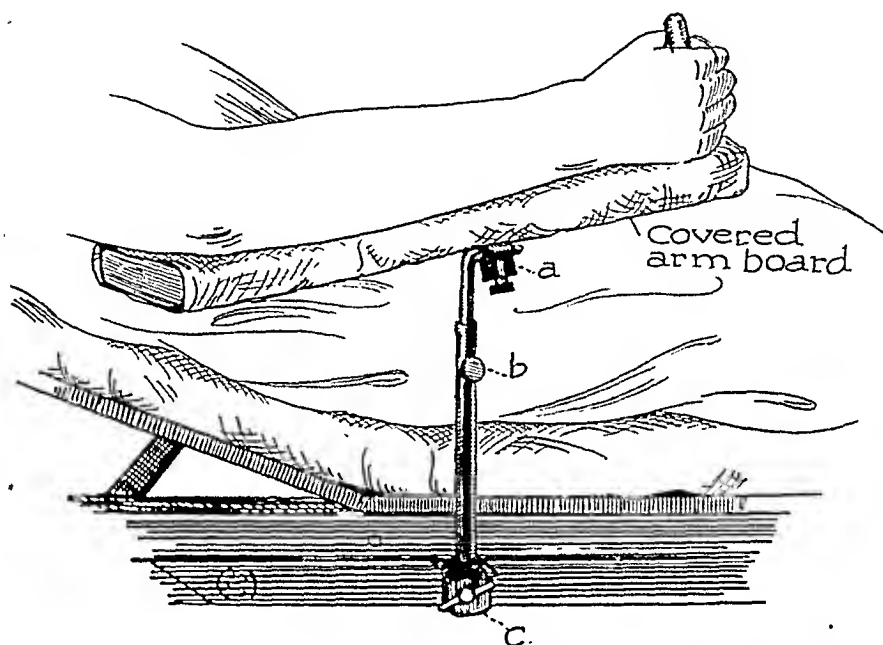


Fig. 11.—The type of arm rest used for study of the finger tips. It is constructed so as to permit adjustments in three directions, thus enabling the part to be brought to heart level and at the same time ensure a comfortable position for the arm.

Measuring the Volume of the Part for Study.—The volume of the part for study can be measured with extreme accuracy by means of negative and positive casts of the part.^{3,4} Measurements of volume to an accuracy of several cubic millimeters are not necessary except for highly specialized experimental work. For ordinary clinical purposes more practical methods of sufficient accuracy can be employed to measure the volume of the part. Two methods of this sort are used in this laboratory:

1. One method (Fig. 5, B) consists of using a cylinder (b) made of lucite with a narrow vertical glass tube (a) fixed along the outer wall of the cylinder and connecting with its lumen near the base. A millimeter scale (c) is placed near the narrow bore tube. The internal diameter of the large cylinder is made of such a size that an increase of 1.0 c.c. in the volume of the liquid contents of the cylinder causes the meniscus in the narrow bore tube to rise 0.5 millimeter. The large cylinder is filled about three-fourths full with water. A detergent such as octyl alcohol is placed over the fluid in the narrow tube in order to prevent the meniscus from sticking. To measure the volume of the part, the entire part

to be enclosed in the extremity cup is submerged in the water within the large cylinder. For example, if the tip of the index finger is to be studied, the tip of the finger is gently submerged into the water in the large cylinder until the level of the water in the large cylinder reaches the level of the major dorsal and palmar skin creases. The linear rise of the meniscus in the narrow tube in millimeters produced by displacing water in the large cylinder determines the volume of the part. Each 0.5 mm. rise is equal to 1.0 c.c. of part. This method is accurate to 0.2 cubic centimeter.

2. Another method (Fig. 5, *A*), accurate to about 0.1 c.c. and just as simple to employ, follows. The large vessel (*a*), placed on a horizontal platform, is filled with water until it overflows into the calibrated (Esmarch) test tube, (*b*). The part to be studied is then gently inserted into the water until the part to be included in the extremity cup is submerged. The water displaced spills into the calibrated test tube and is equal to the volume of the portion of the extremity to be studied.

Connecting the Part to the Plethysmograph.—An extremity cup is selected that fits the part snugly without constricting the part. This is ensured by providing many cups from which to select. The diaphragm through which the part is inserted is shaped by means of a sharp knife to fit properly. The sealing material (printers' roller compound) is heated in hot water (about 150°F.) until it is of such a viscosity that it may be applied with a wooden applicator around the line of junction between the diaphragm in the cup and the part to make an air-tight seal. The same amount of the part is enclosed in the extremity cup as was measured in the volume-measuring cylinder. After the sealing jelly has stiffened with cooling, the rubber tubing leading from the plethysmograph is connected to the metal tube on the diaphragm of the extremity cup. The rubber tubing is then fixed to the dorsum of the hand or foot with a strip of adhesive tape and then fixed again to the forearm or leg. *When the extremity cups are being connected to the parts, the opening and closing valves should be turned to "open."* This connects the pneumatic system to the atmosphere and protects the sensitive metal capsule while the part is being connected to the instrument. This precaution is exceedingly important. By simply turning the valve to the "closed" position, this isolates the pneumatic system and part from the atmosphere at atmospheric pressure. The part is now ready for testing.

Testing for Leaks.—When the pneumatic system is closed off from the atmosphere, the string shadow can be brought into any position with the baseline adjustment (Fig. 6, *16*). It will not remain in a chosen position if there are leaks. When the pneumatic system is opened to the atmosphere, the string will suddenly return to the original resting position.

Standardization of the String.—After the part has been connected for study, the selector control (Fig. 6, *18*) is properly set and the valve for that part is "closed." The string shadow is then brought to the desired position with the baseline adjustment (Fig. 6, *16*). If this is impossible, then there is a leak

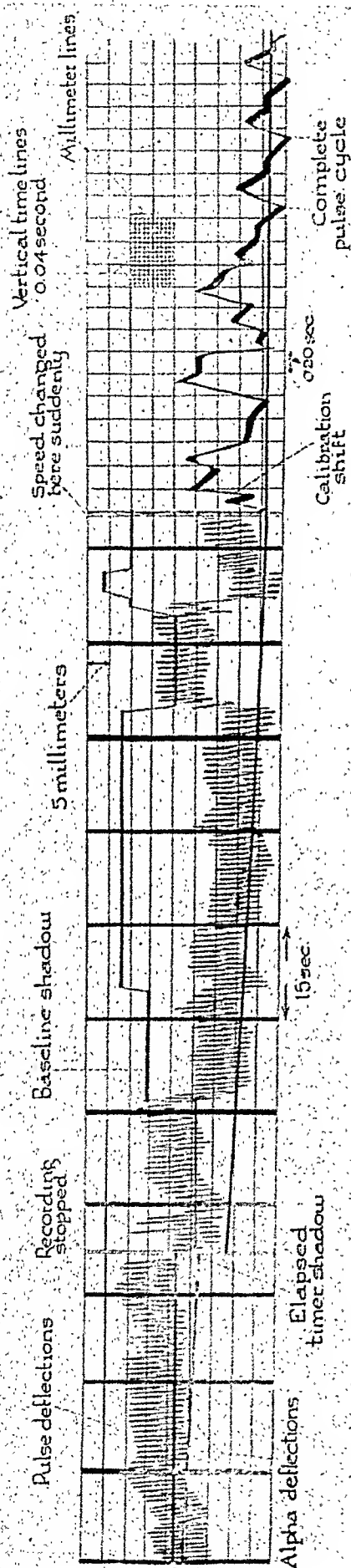
which is usually at the jelly seal at the extremity cup. The string shadow is then focused with the focusing nut (Fig. 6, 19). By pressing on the calibrator lever (Fig. 6, 23) and moving it until it is stopped, a 10.0 c. mm. change in volume is produced. From the already measured volume of the part the string shadow is adjusted in sensitivity until its sensitivity is such that a 10.0 mm. movement of the string shadow occurs per 10.0 c.mm. volume change per 5.0 c.c. of part. Table I indicates the necessary linear movement for the string shadow for various-sized parts. As a result of such a standardization, each millimeter movement of the string shadow on the completed plethysmogram is equal to 1.0 c.mm. change in volume per 5.0 cc. of part. This corrects for variations in size of the part and also eliminates any calculations to reduce recordings to a common unit of measurement. This also makes it possible to read quantitatively the plethysmogram directly.

Taking the Plethysmogram.—Once the proper standardization has been completed, the plethysmogram may be recorded. *The string shadow should be brought to the center of the camera slit at the commencement and the termination of the recording.* This ensures more accurate measurement of gross changes in volume. During the recording of the plethysmogram, the calibrator lever (Fig. 6, 23) should be deflected so as to make an associated record of the standardization for future reference and check. The recording should be made for three or four minutes (longer periods are required to study *gamma* deflections) at the slow camera speed; that is, with the speed change control (Fig. 6, 22) at the *S* position. Should the string shadow tend to move away from the camera slit, it should be returned by means of the baseline adjustment knob (Fig. 6, 16). In order to facilitate the interpretation of the completed plethysmogram, baseline adjustments should be used as infrequently as possible. The string shadow should be allowed to move back and forth spontaneously. If the patient is properly relaxed, baseline adjustments are used relatively little unless the patient is subjected intentionally to a stimulus. It is advisable to terminate each recording with a few seconds of recording at the fast camera speed; that is, with the speed change control (Fig. 6, 22) at the *F* position with one or two associated calibrator lever deflections. This provides an opportunity of studying the morphologic characteristics of the pulse tracing.

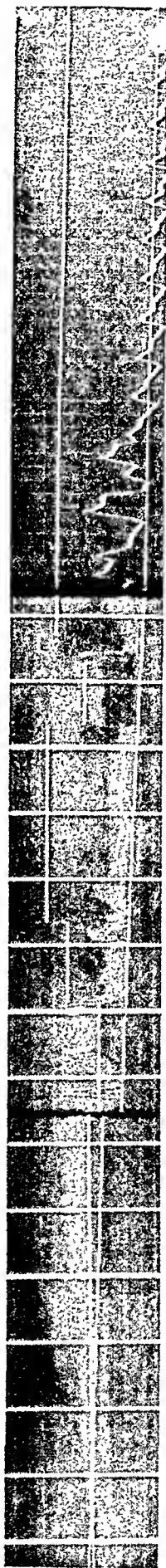
Once the recording has ended, *open all valves to the "open" positions before disconnecting the tubing from the extremity cup.* This protects the sensitive metal capsule which activates the string.

THE PLETHYSMOGRAM

The *plethysmogram*, the completed record of the plethysmograph, is essentially an ordinary type of Cartesian coordinate in which *volume is represented on the ordinate and time on the abscissa.* Fig. 12 shows diagrammatically the various configurations of the data recorded on the plethysmogram. The horizontal millimeter lines and the vertical time lines shown for the rapid camera speed are similar to those employed in clinical electrocardiography. In slow speed records,



A.



B.

Fig. 12.—A is a drawing of a segment of the plethysmogram shown in B. The labelling of A is self-explanatory. It can be seen from these plethysmograms that the *pulse deflections* and *alpha deflections* (the more rapid deflections) are recorded by the bowstring. The *baseline shadow* records gross changes in volume of the part, such as large *beta deflections* and *gamma deflections* and is produced by the pin shadows activated by the baseline adjustment. At the fast speed the configurations of the pulse waves are made evident. It can be seen that when the camera was stopped or turned off for the first time, the elapsed timer shadow had shifted 6 mm. in position by the time the camera had been turned on again. This shift represents a 1.5 minute elapse in time. This elapsed timer makes it possible to keep a record of time even when the camera is turned off. Consult the text for further details.

the time lines occur at fifteen-second intervals with each fourth time line being broader than the others. This facilitates the counting of whole minute intervals of time. Fig. 12 also shows the sensitive string shadow with a pulse wave for each heartbeat. The slow speed record shows the volume of the *pulse wave* very well without detail configurations of this wave. The fast speed record depicts the details of the pulse wave very clearly. Figs. 12 and 13 also show the *alpha waves* or *deflections*, *respiratory deflections*, and *beta deflections*. Portions of *gamma waves* are being traced by the pin shadows of the baseline adjustment or "coarse recorder." The various types of spontaneous variations in volume of the part are discussed later and are shown in Fig. 13. It is seen from Fig. 12 that

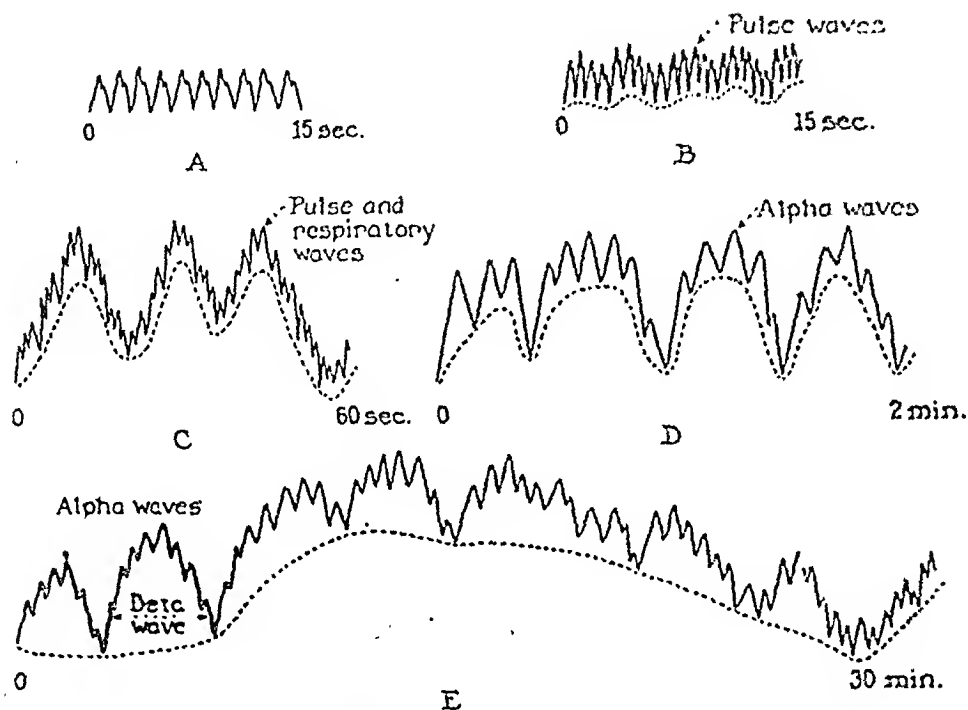


Fig. 13.—Diagram of the five types of spontaneous volume deflections studied to date. They are described in detail in the text.⁹ (From Burch, G. E., Cohn, A. E., and Neumann, C.: *Am. J. Physiol.* 136: 433, 1942.)

whenever the string shadow is changed to a new position by the baseline adjustment, there results a sudden simultaneous change in the position of the string shadow and the pin shadow of the *baseline adjustment*. The baseline indicator rises in the record when an increase in total volume of the part necessitates an adjustment in the baseline and vice versa. The baseline indicator is seen to draw a graph of gross change in volume of the part. The record, therefore, notes sudden small changes in volume of the part (the string record) and any simultaneous large changes in volume of the same part (baseline indicator).

Since the baseline adjustment or gross volume tracing records volume change (1.0 mm. linear movement per cubic millimeter of volume change) regardless of the size of the part under study, it is necessary to reduce the gross

volume change to the standard unit: cubic millimeter of volume change per 5 c.c. of part. This is very simple to do by merely properly labelling the units on the ordinate axis or vertical axis of the completed plethysmogram. The standardization chart shown in Table I can be used for this purpose and thus eliminate the necessity of any calculations. For example, if the part under study has a volume of 3.8 c.mm., then every 10 mm. on the completed plethysmogram is marked off and labelled 13.2 c.mm. (Table I), since each 10 mm. linear change is equal to

TABLE I. FACTORS FOR CORRELATING MOVEMENT OF STRING WITH VOLUME OF PART

In order to have a completed record in which the size of the part is reduced to a common denominator, the sensitivity of the string is varied. The resultant tracing in millimeters is equal to cubic millimeters per 5 c.c. of part. The factors for calibrations are shown. To perform this, the sensitivity of the string is adjusted so that a complete deflection of the calibrator lever produces the indicated linear movement for the various-sized parts.

VOLUME OF PART (C.C.)	MILLIMETERS STRING SHADOW MUST MOVE	VOLUME OF PART (C.C.)	MILLIMETERS STRING SHADOW MUST MOVE
1.0	50.0	5.2	9.6
1.2	41.7	5.4	9.3
1.4	35.7	5.6	8.9
1.6	31.3	5.8	8.6
1.8	27.8	6.0	8.3
2.0	25.0	6.2	8.1
2.2	22.7	6.4	7.8
2.4	20.8	6.6	7.6
2.6	19.2	6.8	7.4
2.8	17.9	7.0	7.1
3.0	16.7	7.2	6.9
3.2	15.6	7.4	6.8
3.4	14.7	7.6	6.6
3.6	13.9	7.8	6.4
3.8	13.2	8.0	6.3
4.0	12.5	8.2	6.1
4.2	11.9	8.4	6.0
4.4	11.4	8.6	5.8
4.6	10.9	8.8	5.7
4.8	10.4	9.0	5.6
5.0	10.0		

13.2 c.mm. change in volume per 5.0 c.c. of part. The *elapsed time indicator shadow* records time that has elapsed during an observation whether the camera is on or off. For example, in Fig. 12, the camera is known to have been turned off during the recording for a period of 1.5 minutes since the elapsed time indicator line moved 6 mm. (4 mm. of movement is equal to sixty seconds) between the time the camera was stopped and started again. The four pins make a complete revolution every hour. Therefore, when the camera is off for continuous periods longer than one hour, one needs only to know the number of whole hours that the camera has been off; periods less than an hour can be calculated from the record.

THE INTERPRETATION OF THE PLETHYSMOGRAM

The plethysmogram is a record of the changes in volume of the part enclosed in the extremity cup in relation to time. The volume changes for the usual periods of time of recording must be due to fluctuations in volume of at least three types of fluid:

1. Blood within the blood vessels
2. Inter- and intracellular fluid
3. Lymph within the lymphatics

In the average patient with the part at heart level it is quite unlikely that variations in volume of the inter- and intracellular fluid contribute very much to the changes in volume except of a special type and under special circumstances⁵ (vide infra). From the behavior of lymphatics it is quite likely that variations in the lymph volume of the part do contribute to the waves or volume deflections of relatively slow frequency^{5,6} (vide infra). In the main, variations in volume of the blood within the part are responsible for the changes in volume of the part. This blood is contained in many kinds of blood vessels: small arteries, arterioles, capillaries, venules, small veins, and arteriovenous shunts of many sorts, including the highly specialized glomus bodies. The volume changes recorded on the completed plethysmogram are the algebraic summation of many volume changes occurring in various degrees and directions in many different portions of the enclosed part. These volume changes are brought about by the integration of many hemodynamic, or physical, chemical, psychoneurogenic, and other physiologic phenomena. The entire process which results in any type of change in volume of a highly specialized organ such as the finger tip is concerned with many complicated and little-known local and systemic physiologic processes. The exact role of the various types of blood vessels in the production of the volume changes is not known. From the present state of knowledge of the function of the various types of peripheral blood vessels, certain functions of each of these is known in general terms only. These generally accepted concepts of function for each of the previously mentioned vessels are applied to the interpretation and application of the plethysmogram with similar precision. A precise interpretation cannot be offered, but many valuable facts have been established. The field for study

is quite fruitful and deserves considerable investigation; in the past it has been limited by inadequate standard methods and apparatus for study.

At the present time certain facts have sufficient importance to warrant discussion.

A. *Types of Spontaneous Variations in Volume of the Part*

If a patient rests quietly in bed in a comfortable environment as described previously, spontaneous changes that occur in the volume of the part result in at least five types of *deflections*. They are (1) pulse waves or deflections, (2) respiratory deflections, (3) alpha deflections, (4) beta deflections, (5) gamma deflections.

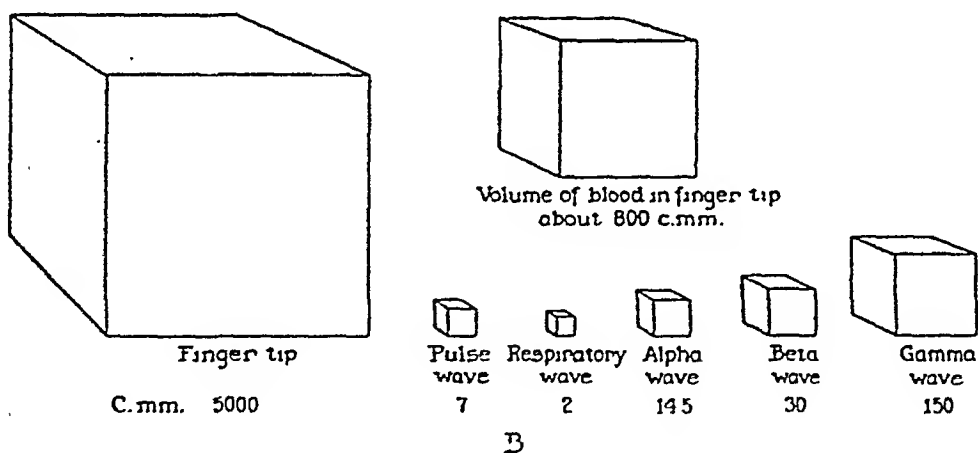
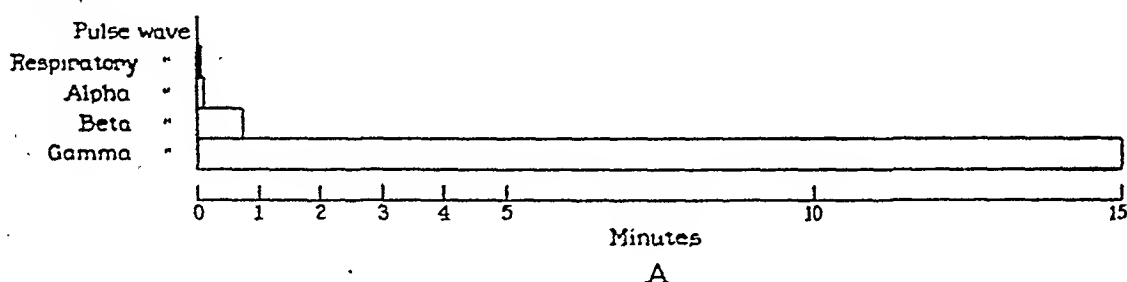


Fig. 14.—Diagrammatic representation of the mean time and volume values of spontaneous volume deflections for the finger tip of the normal adult at rest in a comfortable room.⁹ (From Burch, G. E.; Cohn, A. E., and Neumann, C.: *Am. J. Physiol.* **136**: 433, 1942.)

These volume deflections have been described in detail elsewhere by Burton,⁷ Hertzman and Dillon,⁸ and Burch, Cohn, and Neumann.⁹⁻¹¹ They are illustrated diagrammatically by Figs. 13 and 14. The spontaneous changes that occur in the tips of the fingers and toes range from less than 0.1 to 350 c.mm. or more per 5.0 c.c. of part.* The recognizable volume deflections are as follows:

1. *Pulse Waves or Deflections.*—These are occasioned by the heartbeat and their volume varies markedly (Figs. 12, 13, and 14). There is a definite relationship of volume of the pulse to the alpha wave. The variations in volume

*Henceforth volume changes in a part are given as cubic millimeters per 5 c.c. of part.

for the normal are given in Table II. The mean volumes were 6.9 c.mm. in the finger tips, 4.0 in the toe tips, and 4.1 in the pinnae. The frequency of the pulse deflections varies with the heart rate.

2. *Respiratory Deflections.*—Variations in volume occur with the respiratory cycle (Figs. 12 and 15). They are most highly developed in the pinnae and least developed in the toes. Their rates vary with the respiratory rate. In the normal subject, their volume varies from less than 0.1 to 5.0 cubic millimeters.

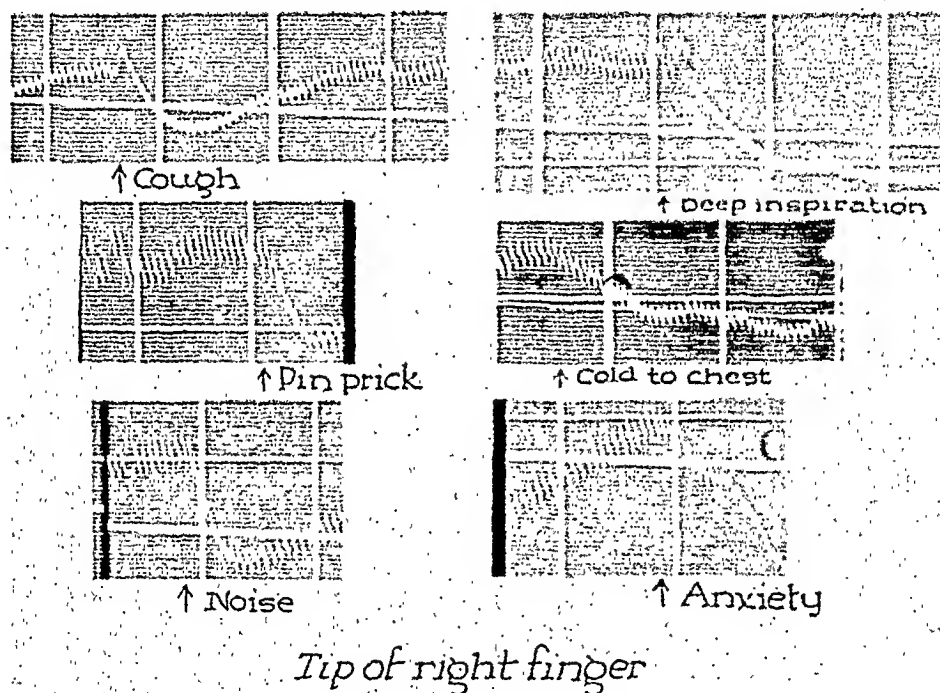


Fig. 15.—Plethysmograms showing vasoconstriction brought about by various stimuli. The first two (cough and deep inspiration) are intrinsic neurogenic stimuli, the second two (pin prick and cold) are extrinsic neurogenic stimuli, and the last two are extrinsic psychogenic stimuli. The anxiety stimulus was brought about by informing the subject, a student, that he had failed a recent examination. These reactions demonstrate the sensitivity of the small peripheral blood vessels to stimuli as well as the potential value of the plethysmograph in the study of neuropsychogenic phenomena. These plethysmograms were recorded at slow camera speed.

A special type of respiratory deflection occurs in the fingers and toes within a few seconds after a deep inspiration. It may present several characteristics:

(a) Following a deep inspiration, there results a spontaneous sudden decrease in volume of the part which is not dependent upon external stimuli (Fig. 15). This varies from 5.0 to 105 cubic millimeters. Associated with this over-all decrease in volume there is a decrease in volume of the pulse waves. After a few pulse beats, vasodilatation begins and continues until the previous pulsatile characteristics are reached. A series of small (2.0 to 8.0 c.mm.) alpha waves appear before the vasodilatation is complete.

(b) The volume changes are more prominent in the fingers than in the toes.

(c) After two or more successive deep inspirations, the degree of response diminishes until no response follows—a sort of tachyphylaxis. The shorter the interval between the deep inspirations, the less the volume change.

(d) The change in the pinnae is not as definite and predictable nor as large as in fingers and toes, nor is it necessarily concordant. There may be either an increase or a decrease.

3. *Alpha Deflections*.—Volume changes less frequent than respiratory deflections are called alpha deflections (Figs. 12, 13, and 15). They are present in all parts and in all people. They vary in frequency and size. They are not uniform, although the contours of the deflections may be smooth. The mean frequency of the deflections is 15.8 per minute in the finger tips, 15.4 in the toes, and 17.2 in the pinnae. The mean volume of the deflections are, respectively, 14.5, 7.1, and 6.6 c.mm. for each part. The variations are shown in Table II, the minimum being less than 0.5 c.mm. and the maximum as great as 81 cubic millimeters. No correlation between frequency and volume necessarily exists.

The volume of the alpha deflections tends to vary in different individuals. These variations and correlations with the pulse waves and the state of the person are discussed below. The alpha deflections are not dependent upon variations in arterial pressure.^{9,12} Sympathectomy or sympathetic nerve blocking will inhibit alpha deflections almost entirely. The alpha deflections in the fingers, toes, and pinnae do not necessarily vary concordantly.¹¹

TABLE II

Quantitative characteristics of the pulse and alpha deflections for the finger tip, toe tip and postero-superior portion of the pinna of twelve resting normal white adults varying from 22 to 65 years of age. Five were women. The room conditions were comfortable.

	VOLUME OF THE DEFLECTIONS OF THE ALPHA WAVES (C.MM. PER 5 C.C. OF PART)		FREQUENCY OF THE DEFLECTIONS OF THE ALPHA WAVES (NUMBER PER MINUTE)			VOLUME OF THE PULSE WAVES (C.MM. PER 5 C.C. OF PART)		
	MEAN	MAXIMUM	MEAN	MAXI- MUM	MINI- MUM	MEAN	MAXI- MUM	MINI- MUM
Finger tip	14.5	81.0	7.9	14	2	6.9	12.4	0.9
Toe tip	7.1	43.4	7.7	13	2	4.0	11.5	0.7
Pinna	6.6	21.0	8.6	13	2	4.1	10.5	0.9

4. *Beta Deflections*.—The succession of alpha waves is superimposed upon large deflections called beta deflections (Figs. 13, 14, and 16). The frequency of these deflections is one to two per minute and the size, 5.0 to 60 cubic millimeters. Beta deflections are exhibited in all parts. Their frequency and volume are totally irregular but tend to vary concordantly in the fingers, toes, and pinnae.

5. *Gamma Deflections.*—These are slowly developing deflections that may reach extensive changes in volume (Figs. 13, 14, and 17). They vary from about one to eight deflections an hour and their size, from about 50 to 350 cubic millimeters. They tend to vary concordantly in the fingers, toes and pinnae, but there is not necessarily a constant relationship.



Tip of Second Right Toe

Fig. 16.—Two complete beta waves or four beta deflections.

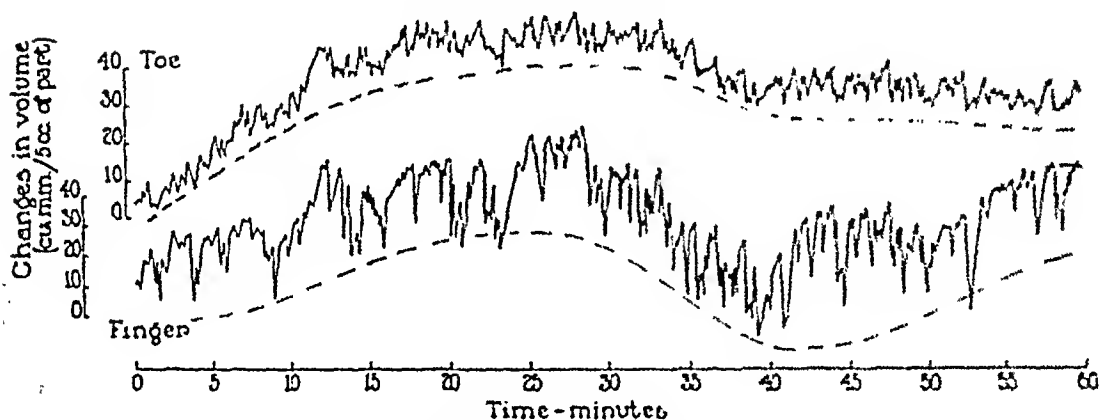


Fig. 17.—Diagrams of a continuous tracing of alpha, beta, and gamma deflections.² (From Rurch, G. E., Cohn, A. E., and Neumann, C.: *Am. J. Physiol.* 136: 433, 1942.)

The deflections are superimposed upon the next slowest type of deflection. There is at least another deflection of a frequency slower than that of the gamma deflection. It has not received any intensive study.

During the course of prolonged studies, variations in room temperature may change the volume of the air within the extremity cup. To study quantitatively the deflections of slow frequency, the room temperature must be controlled. Perspiration occurs at an almost uniform rate under comfortable environmental conditions and therefore only shifts the baseline at a uniform rate without distorting the volume deflections described in the foregoing.

B. Normal Variations in the Plethysmogram

When the subject is resting quietly and comfortably and is relaxed mentally, the pulse and alpha deflections present the normal values of volume and frequency previously described. There are marked variations which can occur

within the normal under certain circumstances which deserve special comment. During some of these conditions the plethysmogram can resemble that found in diseased states and therefore must be adequately appreciated. The discussion below will be mainly limited to the pulse and alpha deflections because only they have received a significant degree of evaluation. The beta and gamma deflections will be mentioned rarely.

Psychic State.—The psychic state of the individual can influence the pulse and alpha deflections greatly (Fig. 15). When the patient is tense, anxious, unhappy in his environment, frightened by the study, or in any way ill at ease, the pulse and alpha deflections will tend to be small in volume and the rate of the pulse deflections is increased by the tachycardia. This type of reaction is due to the increase in vasomotor tone associated with the increase in sympathetic activity related to the psychic disturbance.

Changes in the patient's state of mental tension are reflected by changes in the character of the spontaneous volume deflections. Measurements of these changes may serve^{9,13} as a means of evaluating, in part at least, some aspects of the psychic state of an individual. With flushing or blushing there results a marked increase in the volume of the pulse deflections and an associated decrease in the volume of the alpha deflections. When the patient is comfortable and relaxed and the vascular tone is of an average normal amount, the pulse deflections are of moderate or mean volume and the alpha deflections are of good volume.

Cold.—When the patient's body is chilled by a cool room, or by applying cold locally to any portion of the body, there results a vasoconstriction with a marked reduction in the volume of the pulse and alpha deflections (Fig. 15). The degree of vasoconstriction is more or less proportional to the degree of chilling. Cold is a strong vasoconstrictor stimulus and can be employed as a test of an intact neurovasomotor mechanism. After prolonged chilling, vasodilatation may set in with a resultant increase in volume of these deflections; as a rule the alpha deflections increase in volume to a relatively greater degree than the pulse deflections. Because of the profound influence of chilling upon these deflections, it is necessary to control this factor by making certain that a previously chilled patient has warmed and is comfortable in the room atmosphere. It is well to remember that when there are relatively slight drafts, a resting individual may be chilled even though the dry bulb temperature is within a comfortable range.

With prolonged chilling, the volume of the finger and toe tips decrease slowly and definitely and result in a negative gamma deflection; that is, an over-all decrease in volume of the part. When the part warms again and blood accumulates to restore the blood volume within the part to its original level, a positive gamma deflection is recorded; that is, there is an over-all increase in volume of the part.

Heat.—When the patient's body is heated by a hot room or by applying heat locally to any portion of the body, there results a marked increase in volume

of the pulse deflections with a marked reduction in the alpha deflections (Fig. 18). There is a gradual increase in over-all volume of the part with the inscription of a positive gamma deflection. These changes are the result of marked vasodilatation with an increase in the volume of the local blood "reservoirs" (probably a misnomer). When the body is cooled to basal levels again, the deflections return to normal.

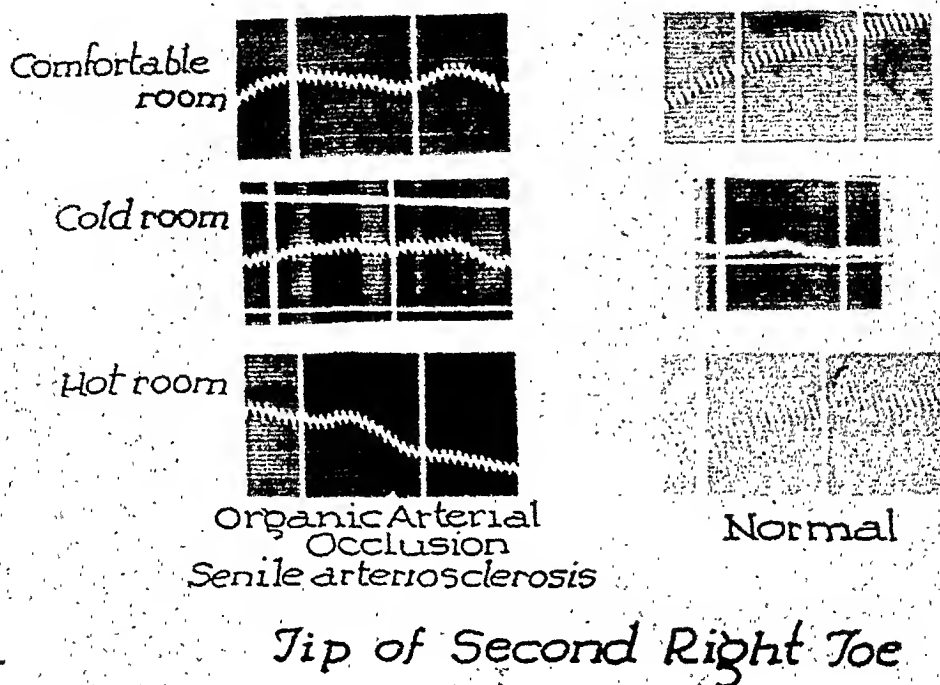


Fig. 18.—An illustration of an isolated use of the plethysmogram in the diagnosis of organic arterial occlusion (obliterating senile arteriosclerotic endarteritis). The volume of the pulse deflections in the comfortable room is considerably less than the normal shown to the right. In the cold room there was a marked vasoconstriction in the normal, evidenced by the marked reduction in size of the pulse deflections. There was only a very slight reaction in the patient with organic arterial occlusion. When the room atmosphere was made very warm to produce vasodilatation, there was essentially no change in the size of the pulse deflections. This indicates a failure or inability to increase the blood flow to the part. On the other hand, the normal subject showed a marked vasodilatation under the influence of the hot room. Such an environment is very strong vasodilatation stimulus. Such a combination of reactions indicate organic arterial obstruction, a fixed circulation, and a marked impairment of the peripheral circulatory reserve. Consult the text for further details of the use of the plethysmogram in disease.

These reactions serve as a good test for organic occlusive arterial and arteriolar disease (Fig. 18). In the presence of occlusive arterial disease, as thromboangiitis obliterans or obliterated arteriosclerotic endarteritis, such vasodilating reactions are impaired or absent (vide infra). The application of heat (45°C.) locally to the torso or to an extremity to produce vasodilatation in the finger or toe tip of another extremity not only tests the patency of the arteries and peripheral blood vessels to that extremity, but also tests the neurovascular reflex mechanism to the part. This is a very useful test clinically for the evaluation of sympathetic activity.

Deep Inspiration.—The vasoconstriction following deep inspiration was described previously when the respiratory deflections were discussed.

Relation of the Part to Heart Level.—When the part is placed below heart level, the volume of the pulse and alpha deflections decrease.¹⁴ The greater the distance below heart level, the greater the decrease in volume of these deflections. As the force of gravity results in the pooling of blood and lymph in the dependent part, a positive gamma deflection is inscribed. The decrease in volume of the pulse and alpha deflections occurs gradually and apparently in direct proportion to the filling of the vessels within the part. The mechanism for the decrease in volume of the pulse deflections remains unknown. Arteriolar vasoconstriction may be a contributing factor. A significant factor is the distention of the vessels with a decrease in further distensibility of the vessel walls.

When the part is elevated above heart level, the volume of the pulse deflections increases markedly and a negative gamma deflection results as the blood within the part drains out. The effect of gravity on the vessels is just the opposite of that produced by lowering the part below heart level. Because of these reactions, it is preferable to keep the part at or near the level of the heart during recordings.

Sympathetic Procaine Block.—Blocking of the sympathetic nerve supply to a finger or toe tip results in a marked increase in the volume of the pulse deflections with an almost complete elimination of the alpha deflections. During the early phases of the interruption of the sympathetic innervation there results an engorgement of the vessels within the part with a resultant positive gamma deflection. The loss of the alpha deflections is to be expected since they are concerned with variations in sympathetic nervous activity.

The use of sympathetic nerve blocking is another important test of arterial patency. Occlusion of the lumen of arteries by organic disease results in an impairment or loss of vasodilatation response to block of the sympathetic innervation to the part.

The finding of vasodilatation following the block of sympathetic nervous pathways in the presence of vascular disease is no indication *ipso facto* that sympathectomy is the therapeutic procedure of choice. In fact, the criteria for the choice of sympathectomy in therapy have never been satisfactorily established.

C. The Plethysmogram in Certain Types of Vascular Disease

The plethysmogram for several types of vascular diseases will be described briefly. A more extensive and detailed discussion is to be reported later.

Obstructive Arterial Disease.—In occlusive diseases of the arteries, such as thromboangiitis obliterans or obliterating arteriosclerotic endarteritis, the volume of the pulse and alpha deflections are reduced (Fig. 18) in proportion to the degree of occlusion of the arteries. In some instances the occlusion may be so complete as to reduce the volume of the pulse deflections to zero. The alpha

deflections are present but markedly reduced in volume and frequency unless there is a complete absence of circulation to the part. Of further diagnostic significance is the reduction in the degree of vasodilatory response to heating the body (generally or locally) or to sympathetic blocking. When the occlusive disease is extensive, there may be no vasodilatation following heating or sympathetic blocking (Fig. 18). The degree of vasodilation (evidenced by the increase in volume of the pulse deflections) following sympathetic nerve block with procaine is an index of the degree of immediate response that may be expected after sympathectomy.

When the occlusive disease is the result of vasospasm or is functional in nature, the pulse and alpha deflections show the same type of change as in organic occlusive disease. However, heating the body or blocking the sympathetic nerves produces a definite and marked vasodilatory response. During the periods between the vasospasm, the alpha and pulse deflections have a normal appearance. This is well exemplified by Raynaud's phenomenon. During the period of syncope or marked arterial spasm there are no pulse and only small alpha deflections, but these return to normal when the spasm is released.

As yet the knowledge of the plethysmogram has not developed to a stage where types of organic or functional occlusive arterial diseases can be differentiated from various entities within each of these two groups. For example, it is not possible to make a diagnostic differentiation between extensive thromboangiitis obliterans and obliterative arteriosclerotic endarteritis merely on the basis of the plethysmogram. It is quite likely that the plethysmograms in these two conditions are entirely different but, with the limited data available at present, no such differentiation can be made.

Vasospastic Peripheral Vascular States.—There are a number of vasospastic states which frequently confront the clinician and must be differentiated. The most frequent one results from anxiety states, simple apprehension, emotional disturbances, and other psychogenic phenomena. These result in small pulse deflections and relatively small alpha deflections. By merely comforting the patient and inducing him to relax by properly discussing his problems, his pulse and alpha deflections return to the average normal values. By a properly arranged observation room,² these vasospastic phenomena can be controlled much more easily. Should difficulty arise in relieving the vasospasm, heating the subject will result in a release.

Vasospastic states or organic vascular diseases associated with vasospastic crises, such as Raynaud's phenomenon, are also characterized by small to absent pulse and alpha deflections; the pulse deflections especially are small. This vasospasm is released by slow local or general heating of the part or body and by sympathetic procaine block. The volume of the pulse and alpha deflections then increase. The sympathetic tone is not necessarily increased above normal in Raynaud's disease. As mentioned previously, such testing differentiates organic obstructive disease from obstruction due to vasospasm.

Arterial Aneurysms.—With the development of an aneurysm of one of the main arteries to a limb, the pulse and alpha deflections are reduced in volume in the digits of the part. The size and nature of these deflections indicate the adequacy of the circulation. The plethysmogram is a better index of the adequacy of the collateral circulation to the part than the oscillometer, for example. Although the plethysmogram will show a reduction in the pulse and alpha deflections of the index finger of the side with an aneurysm, the volume deflections may be fairly good and indicate adequate circulation. On the same patient oscillometric recordings have shown an absence of pulsations in the involved limb. Ligation of the artery proximal to the aneurysm in such a patient has resulted in a clinical cure without untoward peripheral vascular effects.

Thrombophlebitis, Venous Obstruction, and Increased Venous Pressure.—With an increase in venous pressure, regardless of its cause, there is an inverse relationship of the venous hypertension to the volume of the pulse and alpha deflections. The decrease in the volume of these deflections is probably related to a decrease in distensibility of the peripheral vessels as a result of the stretching of their walls by the increased venous pressure and, in some part, to arteriolar constriction. Although the former is more important when the venous pressure is markedly elevated, the relative roles of the two are unknown. Heating the body or sympathetic procaine blocking will release the vasospasm. The amount of release is indicated quantitatively by the degree of increase in volume of the pulse and alpha deflections. The degree of this response is an index of the degree of the immediate clinical vascular response to be expected from sympathetic nerve block or sympathectomy in these conditions.

Miscellaneous Clinical States.—As mentioned at the onset of the discussion of the plethysmogram in vascular diseases, detailed discussions will be published in the near future. Nevertheless, a few more miscellaneous vascular diseases in the clinical management of which the plethysmogram plays a role are:

(1) *Senility*: In the absence of occlusive arterial disease due to arteriosclerosis, uncomplicated senility is usually associated with a slow frequency and large volume of the pulse deflections and relative small volume changes in the alpha deflections. These deflections have been described previously for senility.¹⁵

(2) *Diastolic Hypertension*: This condition tends to be associated with small pulse deflections and fairly well-developed alpha deflections. There are marked variations with considerable overlapping of the normal. The values in several types of diastolic hypertension have been described by Burch, Cohn, and Neumann.¹⁵

(3) *Psychoneurotic States*: Neumann and associates¹³ undertook to employ the plethysmograph in an analysis of the peripheral vascular behavior in emotional states. They found the plethysmogram to vary with the emotional states in a manner which strongly indicates its value in clinical psychiatry.

SUMMARY

A new portable plethysmograph is described which is all metal and, therefore, sturdy and free from the difficulties of deterioration—an important problem when rubber membranes are employed. A device for standardization is incorporated which makes it possible to correct for finger and toe size, thereby resulting in a completed plethysmogram which can be read directly from subject to subject and from time to time in the same subject. This eliminates calculations usually required to convert volume changes to standard units. The plethysmograph also contains a master elapse time recorder which makes it possible to record time even when the camera is off. By means of a baseline adjuster and recorder, gross or large and slow variations in volume of the part can be recorded.

The completed plethysmogram is discussed and five types of spontaneous deflections in volume are considered. The plethysmogram shows the volume changes at slow and fast speeds. The former makes it possible to study all five types of spontaneous deflections in volume, while the latter makes it possible to study the configurations of the pulse wave in detail.

A discussion of the methods of recording the plethysmogram, precautions and possible errors in recording, and its interpretation are given. The use of plethysmography in the study of peripheral vascular disease, psychogenic states, and states of relaxation and tension are briefly indicated. Detailed applications of the plethysmogram to normal and abnormal clinical states will be presented in the near future.

This plethysmograph is a new instrument which is objective, precise, simple, and practical. It has great promise in the study of many problems in health and disease which manifest themselves by disturbances in the blood vessels, lymphatics, and intercellular and intracellular and fluid volumes of the tips of the fingers and toes. By far the greatest number of experimental and clinical applications remain unknown. As with the introduction of any new instrument which has applications in the biologic fields generally and broad use in these fields, the science is in its infancy. It is only with the patient efforts of many investigators, both in the laboratory and the clinic, that the plethysmograph and plethysmogram will develop and reach a state of adequate evaluation and proper usage.

Appreciation is expressed to Mr. G. Morgavi for his technical assistance and excellent machine work which contributed considerably to the development of the plethysmograph.

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FATAL CORONARY ARTERY DISEASE IN YOUNG MEN

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CORONARY artery disease is not generally believed to be a frequent cause of death in people below the age of 40 years. The purpose of this communication is to present nine cases, taken from the records of one Army hospital, of fatal coronary artery disease in young men.

The cases were taken from the protocols of 365 consecutive autopsies, of which 280 were upon patients between the ages of 18 and 40 years. Of these 280 patients, 159 came to autopsy as a result of drowning, trauma, poisoning, shooting, or explosion, a figure much higher than would be expected in the civilian population. The remaining 121 patients died of natural causes. In 7.4 per cent of these 121 patients, autopsy indicated that disease of the coronary arteries was the cause of death. Coronary artery disease accounted for 3.2 per cent of all deaths, including violent deaths, in the 280 patients whose ages ranged from 18 to 40 years.

The cases to be reported are cases in which the only cause of death found at autopsy was disease of the coronary arteries. In no case was coronary disease an incidental finding.

CASE REPORTS

CASE 1.—A 22-year-old soldier was marching in review on June 8, 1942, when he suddenly collapsed and died before a medical officer reached him. A review of his medical record failed to reveal any symptoms suggestive of heart disease. He had never been a patient in this hospital.

Autopsy Findings.—The heart weighed 280 grams. There was no gross abnormality of the myocardium. The anterior descending branch of the left coronary artery contained large, irregular, yellowish plaques throughout its course. These plaques narrowed the lumen of the vessel, most markedly in its proximal portion. Plaques also narrowed the marginal branch of the right coronary artery.

There were numerous plaques beneath the intima of the aorta in its descending portion. The lungs revealed an old scar in the right apex but elsewhere were crepitant in consistency. A moderate amount of frothy blood oozed from the cut surfaces. The liver weighed 1,596 grams and presented no gross abnormality other than slight enlargement.

Microscopically the myocardium showed only cloudy swelling. The coronary arteries revealed marked asymmetrical fibrous thickening and narrowing of the lumina. Cholesterol deposits could be seen in the intima of the vessels. The lungs revealed congestion of the alveolar capillaries, and many of the alveoli were filled with red blood cells and edema fluid. The liver revealed marked congestion of the blood sinusoids.

CASE 2.—On the morning of Jan. 6, 1943, a 33-year-old soldier went through an obstacle course. Upon finishing, he said to a companion, "Gee, that one got me!" Immediately following this, he fell to the ground and died at once. There was no history of recent illness or cardiac disease.

Autopsy Findings.—The heart weighed 308 grams. The myocardium revealed a number of irregular whitish areas which were most numerous beneath the endocardium of the left ventricle. All of the coronary arteries contained atheromatous plaques which produced varying degrees of occlusion. There was extreme narrowing of the anterior descending branch of the left coronary artery, just distal to its point of origin.

There were a few atheromatous plaques in the intima of the aorta. The liver weighed 2,156 grams but was otherwise unremarkable. On cut section there was oozing of frothy material from the lower lobes of the lungs.

Microscopic sections showed fibrosis, degeneration of muscle cells, and mononuclear infiltration in various areas of the myocardium. There were atheromatous plaques in the coronary arteries which showed evidence of calcification. In some sections the lumina of the coronary vessels were greatly narrowed.

The liver showed fatty infiltration. The alveoli of the lungs showed an infiltration of large, mononuclear, pigment-filled cells.

CASE 3.—A 31-year-old artilleryman was last seen alive at 11:30 A.M., Jan. 21, 1943. At this time he seemed to be in good health. At approximately 3:00 P.M., the post medical inspector was called and found the soldier dead in bed. There had been no recent illness or history of cardiac disease.

Autopsy Findings.—The heart weighed 475 grams. On the anterior part of the left ventricle near the apex an irregular pale area was visible. Throughout both left and right coronary arteries many yellowish plaques could be seen. This process was most marked in the circumflex and anterior descending branches of the left coronary. About 1.0 cm. distal to the origin of the anterior descending branch of the left coronary artery the lumen was completely filled with purplish-gray material which could be separated from the wall of the vessel only with difficulty.

The aorta revealed scattered, small, atheromatous plaques in the ascending and descending portions. The liver weighed 2,320 grams but was otherwise grossly normal.

Microscopic study of the coronary arteries revealed atherosclerosis and almost complete occlusion of the left coronary artery. Sections of the myocardium revealed small foci of degeneration in the outer wall of the myocardium of the left ventricle. In addition there was an extensive infiltration of neutrophils and a moderate infiltration of histiocytes.

The liver revealed fatty changes. The aorta revealed atherosclerosis.

CASE 4.—A 31-year-old infantryman had been absent without leave for several days prior to his death. He had been drinking heavily for four or five days. On the morning of Feb. 13, 1943, he was found dead in bed. There was no history of recent illness or cardiac disease.

Autopsy Findings.—The heart weighed 364 grams. The cardiac chambers were dilated and filled with fluid blood. In the left main coronary artery just above its bifurcation there was an irregular, thick, firm, white atheromatous plaque which produced almost complete occlusion of the vessel. About 3.0 cm. distal to the origin of the right coronary artery there was a single plaque similar to that in the left coronary artery. No thrombi could be found.

Several small whitish plaques protruded from the intima of the aorta. The ductus arteriosus was patent and would admit the end of a probe about 2.0 mm. in diameter.

The lungs were heavy and boggy, and dark blood and frothy material oozed from the cut surfaces. A small calcified nodule was present on the pleural surface of the lower lobe of the left lung. The liver weighed 2,170 grams and was flabby in consistency. Just beneath the capsule of the anterior part of the right lobe near its anterior border was an irregular, unencapsulated, soft purple area 3 mm. in diameter.

Microscopic examination of the myocardium revealed fragmentation of muscle cells, patchy fibrosis, and a slight infiltration of neutrophils. Sections of the coronary arteries revealed athero-

sclerosis with calcification which caused marked narrowing of the vessels. Atherosclerosis of the aorta was evident in the microscopic sections.

The lungs revealed marked congestion and many of the alveoli contained large, mononuclear, pigment-bearing cells. The liver revealed fatty changes. In a section made of the small purplish mass many endothelial-lined, blood-filled spaces were seen. This was diagnosed as a hemangioma.

CASE 5.—The history obtained on a 27-year-old soldier was indefinite. Shortly before death, he had been drilling. He was carried to a dispensary, and upon arrival there he was pronounced dead by a medical officer. There was no history of recent illness or cardiac disease.

Autopsy Findings.—The heart weighed 460 grams. The myocardium of the left ventricle was very flabby. In the anterior part of the left ventricle there were many small, irregular, whitish areas, which were more numerous near the endocardial surface. Beneath the endocardium of the posterior portion of the left ventricle were numerous reddish-purple areas which had the appearance of extravasated blood.

There were small sclerotic plaques at each coronary ostium which did not narrow the lumina of the coronary vessels. Numerous large plaques were seen interspersed along the lumina of the larger coronary vessels which narrowed them in many places. Near the origin of the circumflex branch of the left coronary artery the lumen of the branch was filled for a distance of 1 cm. with firm, grayish material. A short distance below the origin of the anterior descending branch of the left coronary artery was a large sclerotic plaque.

The lungs were crepitant and frothy, bloody fluid oozed from the cut surfaces. The liver presented no gross abnormalities and had an estimated weight of 1,500 grams.

Microscopic examination of sections of the myocardium taken from the left ventricle revealed numerous areas of fibrosis. In one section taken from near the endocardial surface, the nuclei of the muscle cells were pyknotic, and the fibers were swollen and pale. In this area there was a marked polymorphonuclear leucocytic infiltration.

The coronary arteries had large atheromatous plaques which narrowed the lumina of the vessels. In a section taken from the completely occluded circumflex branch of the left coronary artery, a recanalized thrombus was evident. Evidence of slight atherosclerosis could be seen in sections of the aorta.

The lungs showed congestion of the capillaries and mononuclear, pigment-filled cells in the alveoli. The liver revealed fatty changes.

CASE 6.—A 34-year-old sergeant was apparently asleep in his barracks on the morning of Jan. 1, 1944. He was heard to gasp and when examined a few minutes later was found to be dead.

Autopsy Findings.—The heart weighed 392 grams. The cardiac chambers were distended with blood. The pericardium over the lower anterior part of the left ventricle covering an area of about 3.0 cm. in diameter was dull and opaque in appearance. The endocardium at a corresponding position was discolored, and the underlying myocardium was yellowish in color and soft in consistency. Throughout the aorta there were numerous sclerotic plaques, and over one of these the endothelium seemed to be absent. This denuded plaque was located in the ascending aorta.

Throughout all of the coronary arteries numerous plaques were present. An especially large plaque nearly obliterated the lumen of the anterior descending branch of the left coronary artery just distal to its origin. Part of this plaque was brownish in color, and opposite it a soft friable blood clot completely obstructed the lumen of the vessel for a distance of about 5.0 millimeters. Just distal to the origin of the right circumflex coronary artery, sclerotic plaques obstructed the lumen. Distal to the plaques the lumen of the vessel was filled with firm, pulpy, purple material which was detached with difficulty.

The lungs were generally crepitant in consistency, and there was a small scar on the surface of the left apex. Blood and frothy material oozed from the cut surfaces. The liver weighed 1,757 grams, and dark blood oozed from the cut surfaces.

Microscopic examination of sections from the left ventricle showed varying degrees of scarring and degeneration. In some areas a slight infiltration of histiocytes and neutrophils could be seen. The anterior descending branch of the left coronary artery showed marked atherosclerosis with fibrosis of the arterial wall. An organizing thrombus was present in this vessel. A section from the proximal part of the right marginal branch revealed that the lumen was completely filled by dense fibrous tissue in which there was a slight infiltration of mononuclear cells.

The aorta showed a fibrous hyaline plaque beneath which the muscular fibers were degenerated. The lungs revealed only moderate congestion and pigment-filled mononuclear cells in the alveoli. The liver showed congestion of the blood sinusoids and fatty infiltration.

CASE 7.—A 38-year-old infantryman had been in the army fifteen months. During that time he had never been on sick call and had never complained of any symptom referable to the cardiovascular system prior to his last illness. On May 3, 1944, he casually remarked to one of his associates that he was having a little difficulty in breathing at times but that this symptom did not trouble him particularly. On the morning of May 4, 1944, he ate breakfast with his company and seemed to feel well at the time. Following breakfast he went to his barracks and sat down on his bed. At about 7:10 A.M. one of the men in the barracks noted that he was lying on the bed apparently unconscious. He was groaning, and, after a few minutes, vomited several times in quick succession. A medical officer was called, and when he arrived at 7:25 A.M. the soldier was dead.

Autopsy Findings.—The heart weighed 364 grams. No areas of scarring could be observed grossly. The chambers were dilated and contained partly clotted blood. The entire left coronary artery proximal to its division contained a large irregular atheromatous plaque with interspersed zones of calcification. The lumen of this artery was slitlike and could be recognized only by moving the walls of the vessel longitudinally. The anterior descending branch of this artery contained a similar plaque extending along the vessel for 1.5 cm. from its point of origin. No other plaques were seen in the other coronary arteries. Only a few minute yellowish flecks were seen in the aorta.

The lungs were crepitant. Beneath the pleura of the left upper lobe two small nodules 3 mm. in diameter, filled with caseous material, were seen. The lungs were not boggy or scarred, and only a small amount of dark blood oozed from the cut surfaces. The liver weighed 2,100 grams. The cut surface was dark yellowish-brown in color, and blood oozed freely from it.

Microscopic study of sections of the coronary arteries revealed marked atherosclerosis. In the section taken from the left main coronary the intimal surface of the plaque was seen to be absent. A small fresh thrombus which did not completely fill the lumen was attached at this denuded point. The section taken from the anterior descending branch presented a similar picture, except that there was no thrombus. The adjoining myocardium revealed no marked changes from normal.

The nodules taken from the left lung were found to have caseous centers surrounded by cellular reactions typical of tuberculosis. No similar lesions were encountered grossly or microscopically in any other organ. The liver showed slight congestion of the blood sinusoids and fatty infiltration.

CASE 8.—On the morning of June 13, 1944, a 27-year-old sergeant was undergoing a test of physical fitness with his company. While on a hike following violent exercise the soldier fell. He was taken immediately to the hospital and upon arrival was found to be dead. There had been no hospital admission previously, and the patient had had a physical examination several weeks previously which revealed no disease. However, the soldier had in his pocket on arrival at the hospital a partly used package of "crush ampules of ammonia" which suggested that he may have had some cardiac symptoms.

Autopsy Findings.—The heart weighed 357 grams and all chambers were filled with partially clotted blood. No areas of scarring or infarction were seen. Just below the origin of the anterior descending branch of the left coronary artery there was a soft symmetrical plaque which reduced

the lumen to about one-third of normal. Below this, in several areas, the walls of the vessel were calcified, but very little thickening was evident. In the circumflex branch of the left coronary artery there were several small soft plaques. Near the origin of the right coronary artery there was a large irregular plaque surrounding the lumen and reducing its caliber.

The intima of the thoracic aorta was flecked with yellowish streaks and spots. The lungs were crepitant in consistency, and only a small amount of dark blood oozed from the cut surface. The liver weighed 2,214 grams, and dark blood oozed freely from the cut surface.

Microscopic sections of the myocardium were normal. Sections taken from the coronary arteries showed marked atherosclerosis with varying degrees of fibrosis and calcification. Sections of the aorta revealed slight irregular lipoidal infiltration of the intima.

Lung sections showed only congestion of the interalveolar capillaries. Sections of the liver showed congestion of the blood sinusoids and fatty infiltration.

CASE 9.—Little history could be obtained on a 39-year-old soldier who, for several days prior to admission, had complained of vague abdominal distress. Shortly before death he was lying on his bed because of abdominal distress. He arose, gasping for breath, and expired suddenly.

Autopsy Findings.—The heart weighed 345 grams. There were no gross abnormalities of the myocardium. The left main coronary artery showed marked thickening and narrowing of the lumen about 1.0 cm. proximal to its bifurcation; the sclerotic process extended along the anterior descending branch throughout its length. The circumflex branch of the left coronary artery for a distance of about 3.0 cm. showed a similar sclerotic process. Numerous plaques were also seen in the right coronary artery.

The aorta revealed atherosclerosis of varying degrees. In the abdominal portion there were numerous thick plaques from which the covering aortic intima seemed to be absent.

The pulmonary arteries showed numerous, irregular, yellowish plaques projecting into the lumina of the vessels. A firm calcified node about 1 cm. in diameter was found in the upper lobe of the left lung. There was no scarring, and the lungs were crepitant. The liver weighed 1,700 grams and was firm in consistency. The brain revealed no cephalomalacia or other abnormality, although the posterior communicating arteries showed numerous intimal plaques which produced no marked narrowing of the vessels.

Microscopic examination of the myocardium revealed a rather diffuse interstitial fibrosis and degenerative changes of the muscle fibers. Sections of the coronary vessels revealed sclerosis which resulted in narrowing of the lumina of the vessels. The aorta showed sclerosis of varying degree with scarring of the media.

The lungs showed numerous mononuclear, pigment-filled cells in the alveoli. A fresh thrombus was seen in one of the smaller pulmonary radicles. The liver cells were well preserved although the blood sinusoids and central veins were moderately congested. Multiple sections of the brain revealed no abnormality.

DISCUSSION

The clinical features of the cases are summarized in Table I.

French and Dock* have called attention to certain clinical features of coronary artery disease in young soldiers. Seventy-three of their eighty patients showed some degree of obesity. In none of the cases which we have reported was obesity mentioned in the autopsy protocols. The estimated weights and actual measurements tabulated in Table I indicate that only one patient (Case 3)

*French, A. J., and Dock, W.: Fatal Coronary Arteriosclerosis in Young Soldiers, J. A. M. A. 124: 1233, 1944.

TABLE I. SUMMARY OF CLINICAL FEATURES IN NINE CASES OF FATAL CORONARY DISEASE

CASE	HEIGHT (INCHES)	WEIGHT (POUNDS) (ESTIMATED)	AGE (YEARS)	SYMPTOMS	ACTIVITY IMMEDIATELY PRECEDING DEATH
1	61	115	22	None	Marching
2	65	135	33	None	Violent exertion
3	69	200	31	None	Lying in bed
4	68	165	27	None	Drunkenness
5	66	160	27	None	Drilling
6	67	145	34	None	Lying in bed
7	67	145	38	Mild dyspnea	Getting up and eating breakfast
8	69	160	27	(?) Relieved by ammonia	Violent exertion
9	68	Well developed and nourished	39	Abdominal distress	Lying in bed

could be considered as markedly obese. It is of interest to note that none of the men was above average height, and there was a tendency in the series toward shortness of stature. This was most marked in the patient in Case 1.

French and Dock failed to find any racial predominance among their cases. All of the nine patients reported on by us had English, Scotch, or Irish names, except one (Case 7). There were no Negroes in the series.

As for precipitating influences, it can be seen that in three instances death occurred while the subjects were at rest; it cannot be stated definitely in every case that the soldiers were not resting because of some symptom. In two cases death occurred immediately after violent exercise; in two, during moderate exercise (marching and drilling); in one, during or after an alcoholic debauch; and in one death occurred on beginning the morning activity.

In only three of the nine cases (Cases 7, 8, and 9) did the records give any indication of even slight symptoms of coronary artery disease before sudden death. It is striking that symptoms were so few and so mild and that not one patient lived to reach the hospital. It is a matter for conjecture whether a thorough medical history taken before the death of the nine soldiers would have revealed symptoms of chest or epigastric discomfort or dyspnea. If such symptoms had been elicited, it is quite possible that they would have been thought inconsequential. I have been impressed by the relative frequency of mild chest or epigastric discomfort of vague character complained of by soldiers in a separation center.

TABLE II. SUMMARY OF PATHOLOGIC FEATURES IN NINE CASES OF FATAL CORONARY DISEASE

CASE	HEART WEIGHT (GRAMS)	LIVER WEIGHT (GRAMS)	CORONARY ARTERIES	MYOCARDIUM	INCIDENTAL FINDINGS
1	280	1,596	Atherosclerosis of anterior descending and right marginal	Cloudy swelling	None
2	308	2,156	All of main branches of coronary arteries sclerotic, with calcification	Fibrosis; degeneration; cellular infiltration	None
3	475	2,320	Marked atherosclerosis of left coronary and its branches	Degeneration; neutrophilic and mononuclear infiltration	None
4	364	2,170	Atherosclerosis of left and right coronary arteries; calcification	Patchy fibrosis; fragmentation of muscle cells; cellular infiltration	Patent ductus arteriosus; small hemangioma of liver
5	460	1,500*	Atherosclerosis, generalized; recanalized thrombus in left circumflex	Fibrosis; hyalinization and cellular infiltration; degeneration	None
6	392	1,757	All of main branches of coronaries sclerotic, most marked in branches of left; fresh thrombus of anterior descending; occlusion of right marginal	Fibrosis; degeneration and cellular infiltration; hyalinization	None
7	364	2,100	Atherosclerosis of left coronary and its branches; fresh thrombosis of left main coronary	No abnormality	Tuberculous focus
8	357	2,214	Sclerosis of main right coronary and branches of left; calcification	No abnormality	None
9	345	1,700	Generalized sclerosis	Fibrosis; degenerative changes; interstitial fatty infiltration	Thrombosis of one of pulmonary artery radicles

*Estimated.

In considering certain pathologic factors, it should be emphasized that there was no valvular heart disease or other pathologic findings which could be considered as even a contributory cause of death.

The pathologic data are summarized in Table II. It should be remembered that the term *infarct* is purposely not used because its use may give the impression that fresh areas of necrosis were seen. In no case was a fresh area of necrosis observed, although all but three of the hearts showed evidence of old infarction.

It can be seen that only two of the hearts (Cases 3 and 5) weighed over 400 grams, although seven of the nine myocardia showed evidence of insult. This is in agreement with the opinion of French and Dock that cardiac hypertrophy is not a marked feature of coronary artery disease in young persons.

In most of the nine cases, the liver showed a moderate degree of enlargement; the weight averaged 1,946 grams. It cannot be stated definitely that this enlargement was secondary to the cardiovascular condition.

The coronary arteries showed all degrees of atherosclerosis. Many contained areas of calcification, hyalinization, cholesterol deposits, and fibrous replacement of the media. In three of the nine cases, thrombosis of one of the coronary arteries was present. Thrombosis occurred in the anterior descending branch of the left coronary artery in one patient, in the main left coronary artery in one, and in the circumflex branch of the left coronary in one patient.

The state of the coronary circulation did not always accurately reflect the state of the myocardium. There were varying degrees of scarring, fibrosis, and cellular infiltration in the myocardia, but in none of the hearts was there seen a fresh, completely necrotic area infiltrated by neutrophils and surrounded by interstitial hemorrhage. Perhaps no fresh infarction had had time to develop since all of the deaths were sudden.

Incidental findings are recorded as a matter of record in Table II and are not emphasized in the case reports for their recounting would be irrelevant.

SUMMARY

1. A detailed report of nine cases of fatal coronary artery disease in men between the ages of 22 and 40 years is made.
2. These nine cases comprised 3.2 per cent of all autopsies, a total of 280, performed on men between 18 and 40 years of age.
3. The nine cases comprised 7.4 per cent of all autopsies, a total of 121, performed on men between the ages of 18 and 40 years who died of natural causes.
4. Very few of these nine young men gave evidence of having had symptoms of coronary disease before the fatal episode.
5. Death was sudden and unheralded.
6. Most of the nine young men who died of coronary artery disease were of average or below average height.
7. Cardiac weight did not reflect the seriousness of the cardiac condition. Slight to moderate enlargement of the liver may have been related to the cardiac disease.
8. Evidence of old myocardial injury is frequent; evidence of fresh infarction is rare in young men dying of coronary artery disease.

THE EFFECT OF SULFONAMIDE ADMINISTRATION ON CARDIAC FUNCTION IN THE DOG

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SEVERAL reports on the histopathologic effects of the sulfonamides upon cardiac muscle have appeared in the literature, but very few have dealt with the physiologic effects, in spite of the extensive clinical use of these compounds.

While the kidney and liver were frequently the site of histopathologic changes in the experimental studies on toxicity, only a few reports showed cardiac involvement. Nelson¹ examined the tissues in a large series of rabbits and hens which were given fatal doses of sulfanilamide. In twenty-six rabbit hearts examined, twenty-five were normal although other organs showed marked changes, while in seventeen hen hearts, twelve were normal and five showed some slight myocardial change. Maisel, McSwain, and Glenn² studied the effects of sulfadiazine on dogs and found histologic changes in the myocardium in only three of the fourteen treated animals. In man, French and Weller,³ in a critical survey of the necropsy findings in 238 patients who were given sulfonamide therapy shortly before death, reported 126 instances of interstitial myocarditis "rich in eosinophil cells." No correlation could be made between the duration and intensity of therapy with the extent of the myocardial lesions. They succeeded in producing a similar lesion in thirty-eight of sixty mice and thirty-three of forty-seven rats given daily intraperitoneal injections of various sulfonamides in amounts slightly less than the usual clinical dose. In this series, the frequency of the lesion increased with the duration of the treatment. Lederer and Rosenblatt⁴ reported four cases of "sulfathiazole death" in which two cases showed "areas of focal necrosis" in the myocardium. Rich⁵ reported on a patient in whom sulfathiazole was administered as a prophylactic measure before operation for squamous-cell carcinoma. Widespread fresh lesions of periarteritis nodosa were found at autopsy in the heart and other viscera on microscopic examination, although no significant lesions were noted macroscopically. In addition to these vascular lesions, there was a "diffuse inflammatory infiltration of the myocardium" closely resembling that described by French and Weller³ in their patients treated with sulfonamides. This case presents further support for Rich's previous suggestion⁶ that vascular lesions of the periarteritis nodosa type are the

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result of an anaphylactic type of hypersensitivity reaction to some sensitizing antigen—in this case, the sulfonamides.

Attention was first directed toward possible functional cardiac effects during sulfonamide therapy in man by Dozzi⁷ who reported the occurrence of "transient nodal rhythm" in a 27-year-old physician, who was subject to occasional attacks of paroxysmal tachycardia, following a single massive dose of sulfanilamide for a throat infection. An electrocardiogram was taken when the patient complained of cardiac irregularity and this showed a rapid A-V nodal rhythm. Scheinberg and Ingle⁸ reported a case "suggestive of myocardial sulfanilamide myocarditis" since the electrocardiogram showed prolongation of both P-R and QRS intervals with left ventricular predominance. The absence of electrocardiograms taken before and after chemotherapy for comparison makes it difficult to evaluate these findings. Frist,⁹ in analyzing the effects of sulfonamides in 186 patients, reported "cardiac involvement" in two patients given sulfathiazole. Only one case was described and the electrocardiogram showed bundle branch block. The case history revealed that the patient had been given five courses of "sulfonamide compounds" in a period of nine months with severe toxic reactions with each course. After the third course, he complained of fatigue and dyspnea on exertion, and after the fifth course, increased dyspnea, abdominal swelling, ankle edema, and increased weight. Four months later he was hospitalized because of frank heart failure and because the electrocardiogram revealed bundle branch block. At autopsy the heart showed "myocardial hypertrophy with degeneration, fibrosis of anterior wall of each ventricle and of the septum, and extensive mural thrombosis." Microscopic examination showed infiltration and proliferative changes in the myocardium.

Other evidence of functional involvement, but not accompanied by electrocardiographic findings, have appeared in several reports. Hoyne and Larimore¹⁰ reported heart sounds "that were distant and of poor quality though no murmurs were present" after prolonged sulfathiazole therapy in a previously healthy man who had acute agranulocytosis. "Distinctive cloudy swelling of the myocardium" was found at autopsy. Browne, Marvin, and Smith¹¹ reported transient sinus bradycardia (under 60 beats per minute) in 63 of 100 consecutive cases of pneumonia in which the patients were treated with sulfadiazine. This bradycardia developed two to four days after the return to normal temperature and lasted one to four days. In seven cases the heart rate was below 40. Wells and Sax¹² reported "heart sounds that were distant and of poor quality but no murmurs" in a patient who died suddenly following ten days of sulfadiazine therapy. Histologic changes typical of a "diffuse form of isolated myocarditis" were found at autopsy.

Morphologic changes in the heart, of the magnitude reported in these studies, might well be expected to produce functional changes which would be reflected in the electrocardiogram. Although cardiac involvement is not a constant finding during sulfonamide administration, its incidence is frequent enough to warrant investigation. This study was therefore organized to investigate the effects of various sulfonamides, given in doses comparable to those used clinically, upon

cardiac function as revealed by the electrocardiogram. In the first part of the study, presented in a preliminary report,¹³ the sulfonamides used produced no permanent effect on the electrocardiogram, although two dogs showed a transient effect; namely, occasional premature systoles during treatment. Rate changes varied.

PROCEDURE

Mongrel female dogs whose body weight averaged 8 kilograms were used. The animals were carefully selected and in excellent condition during the control period before starting medication.

The drugs studied were sodium sulfathiazole, sodium sulfadiazine, sodium sulfapyridine, sodium sulfamerazine, and sodium sulfapyrazine. In order to insure a maximal effect of the drug, the method described in the previous report was altered somewhat by lengthening the period of drug administration. No twenty-four hour experiments were made in this series.

The drugs were administered by intraperitoneal injection in courses of four doses each, given daily; a rest period of at least one week was allowed after each course.

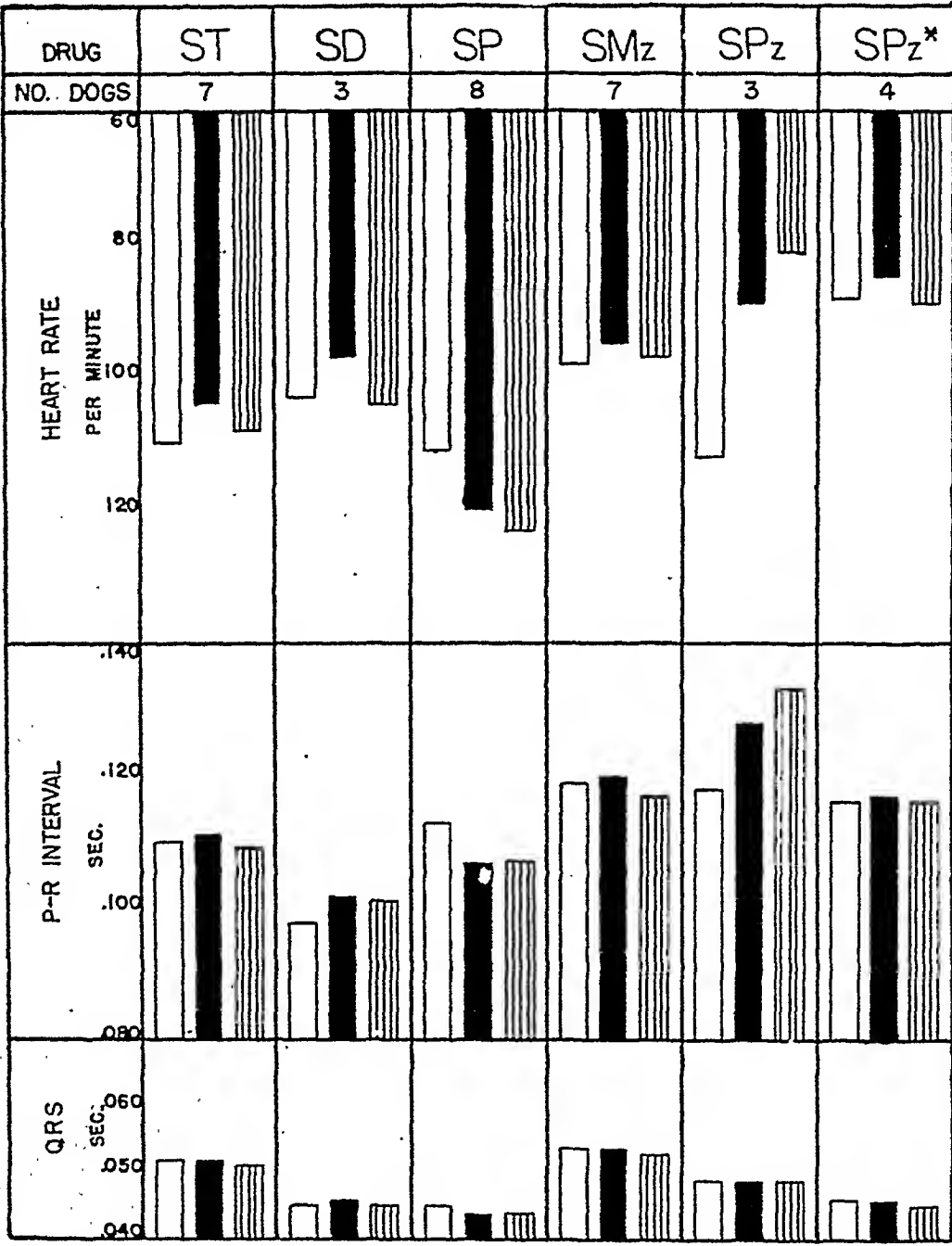
A standard dose was used throughout, a total of 0.65 Gm. per kilogram of body weight for each course of treatment: 0.2 Gm. per kilogram as the initial dose and 0.15 Gm. per kilogram thereafter. This method was chosen rather than attempting to keep a standard blood level because of the wide variation in absorption and excretion in individual animals. While this insured a therapeutic level, in some cases in which the more slowly excreted sulfonamides were used, the level rose well above the therapeutic standard (Table I). This was especially true of sodium sulfapyrazine in which the slow excretion rate resulted in blood levels that caused such a high mortality rate that a lighter dose had to be chosen in order to carry the animals through the entire four courses of treatment (Table II). The total dose was therefore lowered to 0.45 Gm. per kilogram, given in divided doses over four days.

The unanesthetized dogs were trained to lie quietly on their left side while the electrocardiogram (Lead II) was taken. This position was maintained routinely throughout the study. A Hindle No. 3 electrocardiograph was used.

From eight to sixteen control tracings were taken on each animal during the two-week preliminary observation period. During medication two tracings were taken daily, one in the morning just before injection and the second three and one-half to four hours after injection. The blood sample for drug determination was usually drawn immediately after the second tracing. Three to five electrocardiograms were taken at intervals during the rest periods between drug courses and after the fourth course until the drug had disappeared from the blood.

The tracings were analyzed for rate, abnormalities in rhythm, P-R interval, QRS and T waves, and position of S-T segment. Any deviation from the normal electrocardiogram was carefully recorded. The average values obtained from each dog's control tracings were used as a basis for the comparison of effects of medication in that animal.

Since this detailed analysis of the electrocardiograms of Series I was not included in our preliminary report,¹³ this has been summarized with the analysis of Series II and is included in Table I and Fig. 1 of this paper.



*Refers to dogs given light dose.

Fig. 1.—Summary of electrocardiographic findings on dogs given various sulfonamides which survived two or more courses of the drug. Correlation of rate and P-R and QRS intervals during control period, white columns; drug administration, solid columns; and recovery, striped columns.

RESULTS

Control Electrocardiograms.—In the dogs having a “normal” electrocardiogram, the heart rate ranged from 62 to 141 per minute; the P-R interval, from 0.134 to 0.091 second; and the QRS duration, from 0.059 to 0.026 second.

TABLE I. SUMMARY OF ELECTROCARDIOGRAPHIC FINDINGS IN DOGS GIVEN CERTAIN SULFONAMIDES (ANALYSIS OF LEAD II IN THIRTY-NINE DOGS)

DRUG	DOG	DOSES	CONTROL					DURING MEDICATION					AFTER MEDICATION				SUMMARY
			RATE (MIN.)	P-R (SEC.)	QRS (SEC.)	T ₂ WAVES	OTHER ECG CHARACTERISTICS	RATE (MIN.)	P-R (SEC.)	QRS (SEC.)	BLOOD LEVEL (MG. %)	EFFECT ON ECG	RATE (MIN.)	P-R (SEC.)	QRS (SEC.)	T ₂ WAVES	
Sodium sulfam- erazine	12	16	100	.097	.052	T -	S-T negative	122	.092	.050	33.0	Rate rise only change	111	.095	.052	T -	No change from control ECG
	15	16	93	.109	.056	T ±	S-T negative; marked sinus arrhythmia	104	.105	.056	41.0	Rate rise only change	114	.102	.056	T ±	Rate increase only change in ECG
	16	16	98	.114	.058	T -	S-T markedly de- pressed; prolonged P-R	83	.131	.059	37.0	P-R frequently in- creased (.132; .144); rate fell	101	.124	.058	T -	Prolonged conduction time only change from control ECG
	20	16	92	.122	.045	T +	"Normal"	79	.129	.046	25.0	Rate fall only change	89	.120	.044	T +	No change from control ECG
	21	16	100	.131	.052	T -	Prolonged P-R interval with A-V block	81	.127	.050	33.6	Rate fall only change	81	.127	.050	T -	Rate decrease only change in ECG; degree of A-V block un- affected by drug
Sodium sulfam- pyrazine	22	16	100	.119	.061	T +	Slurred S	89	.119	.061	32.6	Elevated S-T segment T ₂ ; T -	92	.116	.059	T +	T and S-T segment changes dis- appear
	23	16	103	.138	.051	T -	Deep S; prolonged P-R interval with A-V block	107	.135	.051	25.0	Slight rate rise only change	90	.137	.050	T -	Rate decrease only change in ECG; degree of A-V block un- affected by drug
	14	16	113	.119	.044	T ±	"Normal"	91	.125	.044	56.6	T wave +; marked rate decrease	84	.130	.044	T ±	Marked rate decrease only change in ECG
	10	12	116	.115	.051	T +; T ±	"Normal"	90	.124	.051	57.5	Marked rate decrease only change	78	.130	.051	T +; T ±	Marked rate decrease only change in ECG

Sodium sulfapyrazine —Cont'd	8	8	106	.121	.052	T-; ±; +	Prolonged P-R interval	86	.135	.052	80.0	Marked rate decrease only change	81	.138	.052	T-; ±; +	Marked rate decrease only change in ECG
	9	8	112	.132	.052	T+	Prolonged P-R interval	106	.124	.052	84.7	Rate decrease, S-T segment depressed and T± after Doso 5 until death	104	.120	.052	T±	Rate fall; S-T segment depressed and T diphasic up to time of death
	17	4	101	.127	.048	T+	"Normal"	83	.125	.051	70.0	Marked rate decrease only change	98	.124	.049	T+	No change from control ECG despite severe drug reaction
	18	4	135	.103	.047	T+	"Normal"	83	.119	.046	69.0	Marked rate decrease only change	59	.134	.045	T+	Marked rate decrease only change in ECG; dog died
	19	4	129	.114	.054	T-	"Normal"	104	.134	.053	88.0	Marked rate decrease only change	—	—	—	T-	Marked rate decrease only change in ECG; dog died
	24*	16	84	.111	.043	T+	"Normal"	84	.114	.044	41.8	S-T segment depressed; T-; P-R interval increased	83	.114	.044	T+	Prolonged P-R interval persists though S-T segment and T waves return to normal
	25*	16	97	.108	.042	T+	"Normal"	93	.109	.042	44.5	S-T segment depressed and T± in most tracings	99	.109	.041	T±	Depression of S-T segment and diphasic T waves persist
	26*	16	88	.115	.039	T+	"Normal"	88	.111	.038	52.5	No change	93	.109	.037	T+	No change from control ECG
	27*	16	83	.128	.059	T+	"Normal"	76	.134	.059	46.0	Slight rate decrease only change	81	.131	.059	T+	No change from control ECG
	2	16	141	.097	.045	T-	"Normal"	130	.101	.044	16.6	Rate fall only change	125	.101	.041	T-	Rate decrease only change in ECG
Sodium sulfathiazole	7	12	111	.106	.059	T-	S-T segment negative	109	.105	.059	9.0	No change	108	.106	.058	T-	No change from control ECG
	1a	14	62	.134	.044	T±	"Normal"	75	.130	.044	—	Rate rise only change	79	.126	.044	T±	Rate increase only change in ECG
	2a	14	133	.108	.036	T±	S-T segment negative; marked sinus arrhythmia	122	.196	.036	—	Rate fall only change	120	.106	.036	T±	Rate decrease only change in ECG

*Light dose. See Table II.

TABLE I. SUMMARY OF ELECTROCARDIOGRAPHIC FINDINGS IN DOGS GIVEN CERTAIN SULFONAMIDES (ANALYSIS OF LEAD II IN THIRTY-NINE DOGS)—CONT'D

DRUG	DOG	DOSES	CONTROL					DURING MEDICATION					AFTER MEDICATION				SUMMARY
			RATE (MIN.)	P-R (SEC.)	QRS (SEC.)	T ₂ WAVES	OTHER ECG CHARACTERISTICS	RATE (MIN.)	P-R (SEC.)	QRS (SEC.)	BLOOD LEVEL (MG. %)	EFFECT ON ECG	RATE (MIN.)	P-R (SEC.)	QRS (SEC.)	T ₂ WAVES	
Sodium sulfa- thiazole —Cont'd	3a	11	92	.116	.045	T ±	S-T segment negative	73	.120	.044	—	Marked rate fall only change	83	.122	.044	T ±	Rate decrease only change in ECG
	4a	8	110	.106	.028	T —	"Normal"; very short QRS	100	.104	.029	—	Rate decrease only change	98	.101	.028	T —	Rate decrease only change in ECG
	5a	8	123	.106	.027	T —	"Normal"; very short QRS	121	.109	.028	—	No change	142*	.102	.027	T —	Rate increase after drug only change in ECG*
Sodium sulfa- diazine	1	16	103	.104	.045	T ±	S-T segment negative	100	.108	.049	72.0	No change	102	.108	.045	T ±	No change from control ECG
	3	16	108	.091	.044	T —	"Normal"	95	.099	.045	60.0	Marked rate decrease only change	101	.097	.045	T —	No change from control ECG
	4	16	99	.099	.045	T —	"Normal"	95	.099	.045	45.5	No change	108	.098	.045	T —	No change from control ECG
	6a	10	77	.123	.035	T +	"Normal"	80	.119	.035	—	No change	79	.127	.037	T +	No change from control ECG though dog died after Dose 10 during Course 2
	7a	5	89	.120	.038	T —	"Normal"	92	.121	.038	—	No change	131	.106	.037	T —	Marked rate increase, dog very ill; died 6 days after Dose 5; no change in ECG complex
	8a	4	108	.110	.036	T —	"Normal"	113	.099	.036	—	No change	98	.110	.036	T —	No change from control ECG

Sodium sulfa- pyridine	10a	17	102	.131	.039	T -; ±; +	"Normal"	108	.126	.038	—	Slight rate increase	109	.124	.038	T -; ±; +	No change from control ECG
	11a	17	85	.128	.040	T -	"Normal"	106	.119	.040	—	Rate rise only change	99	.120	.040	T -	Rate rise only change in ECG
	5	16	125	.094	.037	T ±	S-T negative	130	.090	.036	8.8	Slight rate increase	125	.090	.036	T ±	No change from control ECG
	6	16	113	.110	.052	T +; T ±	"Normal"	130	.096	.052	10.0	Rate rise only change	125	.098	.052	T +; T ±	Marked rate increase only change in ECG
	12a	10	124	.117	.034	T -	"Normal"	157	.100	.034	—	Rate rise only change	165	.098	.034	T -	Marked rate increase only change in ECG
	13a	8	132	.104	.042	T -; T +	"Normal"	108	.108	.042	—	Rate fell; S-T de- pressed and T - in some cases	119	.109	.041	T -; T +	Rate decrease; S-T segment and T waves return to control
	14a	8	98	.112	.037	T -	"Normal"	97	.109	.037	—	S-T segment depressed in some cases	108	.106	.035	T -	S-T and T wave return to "normal"; rate rise only change
	15a	11	110	.108	.026	T +; ±; -	"Normal"; very short QRS	121	.108	.026	—	Rate rise	119	.107	.026	T +; ±; -	Rate rise only change in ECG

*Average of only two tracings.

TABLE II. MILLIGRAMS PER CENT OF FREE SODIUM SULFAPYRAZINE IN BLOOD OF DOGS AT TWO DOSE LEVELS

LIGHT DOSE (0.45 GM./KG./COURSE)						HEAVY DOSE (0.65 GM./KG./COURSE)								
DOG	24	25	26	27	DOG	14	10	8	9	17	18	19		
Control	0.8	0.7	0.7	0.7	Control	1.5	0.5	0.4	0.4	0.4	0.3	0.5		
After Dose 4	52.9	53.9	56.3	51.9	After Dose 4	67.4	38.1	64.8	58.1	70.3	75.0	89.1		
Ten days after Dose 4	3.6	4.2	1.9	2.5	Before Dose 5	9.9	1.4	15.1	25.3					
After Dose 8	47.1	43.4	41.7	49.6	After Dose 8	80.7	85.7	95.2	111.4					
Eleven days after Dose 8	0.8	0.8	1.0	2.8	Four days after Dose 8	—	49.6	64.1	83.0 (Died)					
After Dose 12	35.9	28.5	47.9	31.1	Twenty-five days after Dose 8	31.1	0.5	3.1 (Sick)		Died eight days later; blood level, 37.9	Died seven days later; blood level, 40.2	Died one day later		
Eleven days after Dose 12	0.5	0.8	1.2	1.1	After Dose 12	—	48.9 (Sick)							
After Dose 16	30.6	52.0	64.4	51.6	After Dose 16	111.7	Dogs so ill drug dis-continued							
Eleven days after Dose 16	0.5	7.1	1.2	1.2	Eighteen days after Dose 16	42.9								

Fourteen of the thirty-nine animals showed abnormalities in their control electrocardiograms such as pronounced sinus arrhythmias (two); prolonged conduction time (five); A-V block (two); S-T segment deviation (nine); and slurred S waves (two). T waves were variable. The appearance of negative T waves in Lead II is a common occurrence in the dog electrocardiogram and is not considered of pathologic significance. The rate ranged from 92 to 133; the P-R interval, from 0.094 to 0.138 second; and the QRS duration from .061 to .036 second.

Sulfathiazole.—In the seven dogs given sulfathiazole, three of which showed depression of the S-T segment in their controls, no change occurred in the electrocardiogram during or after medication. While four dogs showed a fall in rate, the marked increase in Dog 5a after drug administration is misleading (Table I) since this is an average of only two tracings.

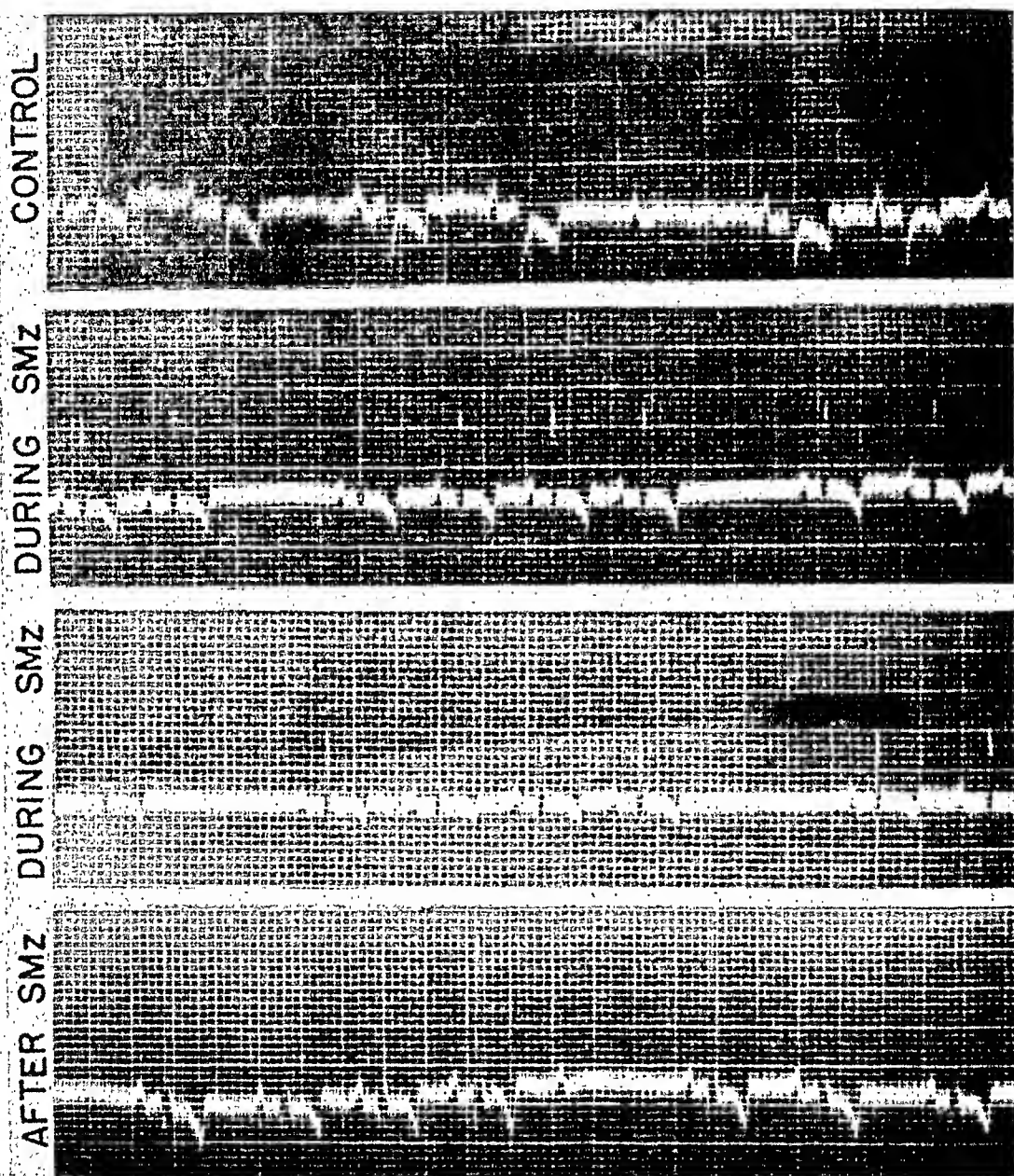
Sulfadiazine.—In the six dogs given sulfadiazine, only one of which showed depression of the S-T segment in the controls, no change occurred in the electrocardiogram following drug administration. This is especially significant since Dogs 6a and 7a (Fig. 4) died after Doses 10 and 5, respectively. Both dogs were very ill and lost weight during medication.

Sulfapyridine.—Of the eight dogs to which sulfapyridine was given, only one of which showed depression of the S-T segment, transient electrocardiographic changes in the form of depression of the S-T segment and inversion of the T wave occurred during medication in Dogs 13a and 14a. These changes disappeared after stopping the drug. An increased rate occurred in seven dogs.

Sulfamerazine.—Of the seven dogs given sulfamerazine, only one had a "normal" control electrocardiogram. Three dogs showed depression of the S-T segment, three showed prolonged P-R intervals, and two of these, Dogs 21 and 23 (Fig. 2), showed A-V block, while Dog 22 had a long QRS complex with slurring of the S waves. This group of animals showing definite cardiac abnormality seems especially interesting since the excretion rate of sulfamerazine is so slow that a consistently high blood level can be maintained during medication. Every dog showed an average blood drug level above 25 mg. per cent during each course of the drug and Dog 15 averaged 41 mg. per cent (Table I). All animals showed some toxic effects during medication including nausea, vomiting, and anorexia.

In spite of the evidence of toxicity, no permanent changes occurred in the electrocardiogram. The degree of block shown by Dog 21 during the control period was not increased by sulfamerazine, and dropped beats occurred (Fig. 2) throughout the experiment. Dog 23 (Fig. 2), whose control showed a greater degree of A-V block since dropped beats occurred in a 5:4 and 4:3 ratio, showed no change with the drug. Wenckebach periods (0.132, 0.136, 0.156, 0.160 second) were present throughout. Dog 22, however, whose control electrocardiogram showed a slurred S wave with a relatively long QRS complex, showed elevation of the S-T segment and a change in the direction of the T wave on some days during medication. These changes disappeared after the drug was stopped.

Sulfapyrazine.—Of the eleven dogs to which sulfapyrazine was given, two showed prolonged P-R intervals, while the others had "normal" control electrocardiograms.

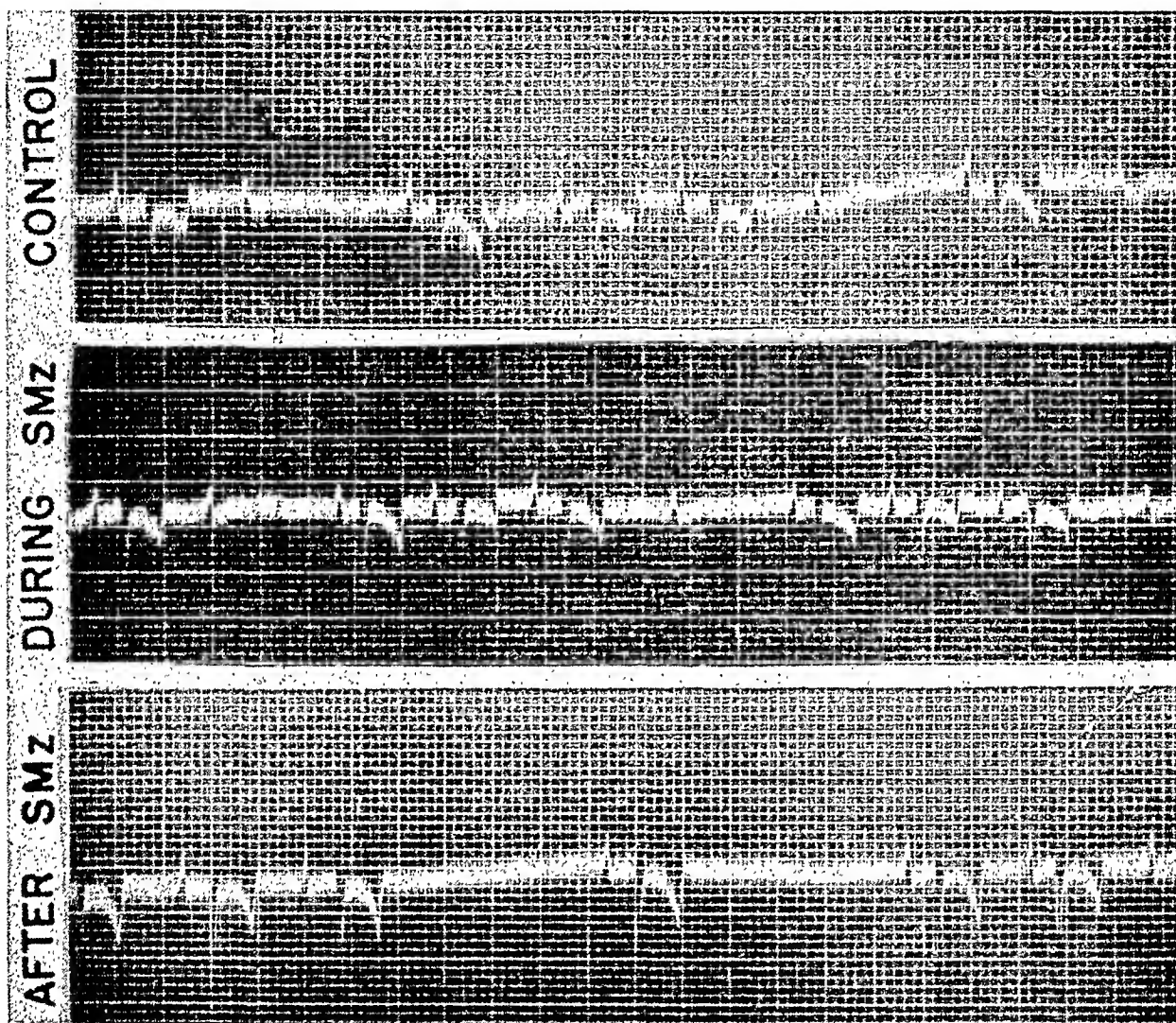


A.

Fig. 2.—Effect of sulfamerazine. A, Three tracings of Lead II from Dog 21 who had conduction defects, prolonged P-R intervals, and A-V block. Four courses of the drug did not affect the degree of block and no change occurred in the electrocardiogram.

B, Three tracings of Lead II from Dog 23 who had pronounced block showing Wenckebach periods (0.112 second, .128 second, and .136 second) in the control. The degree of block was unaffected by four courses of the drug and no change occurred in the electrocardiogram.

The drug, in the 0.2 Gm. dose, was so slowly excreted and proved so toxic that four of the seven dogs died after the first course, and the drug had to be discontinued after Course 2 and after Course 3 in Dogs 8 and 12. Only one, Dog 14, survived the full course of sixteen doses. Because of this high mortality, the smaller dose was used on the remaining four dogs. Drug elimination in these two groups is shown in Table II.

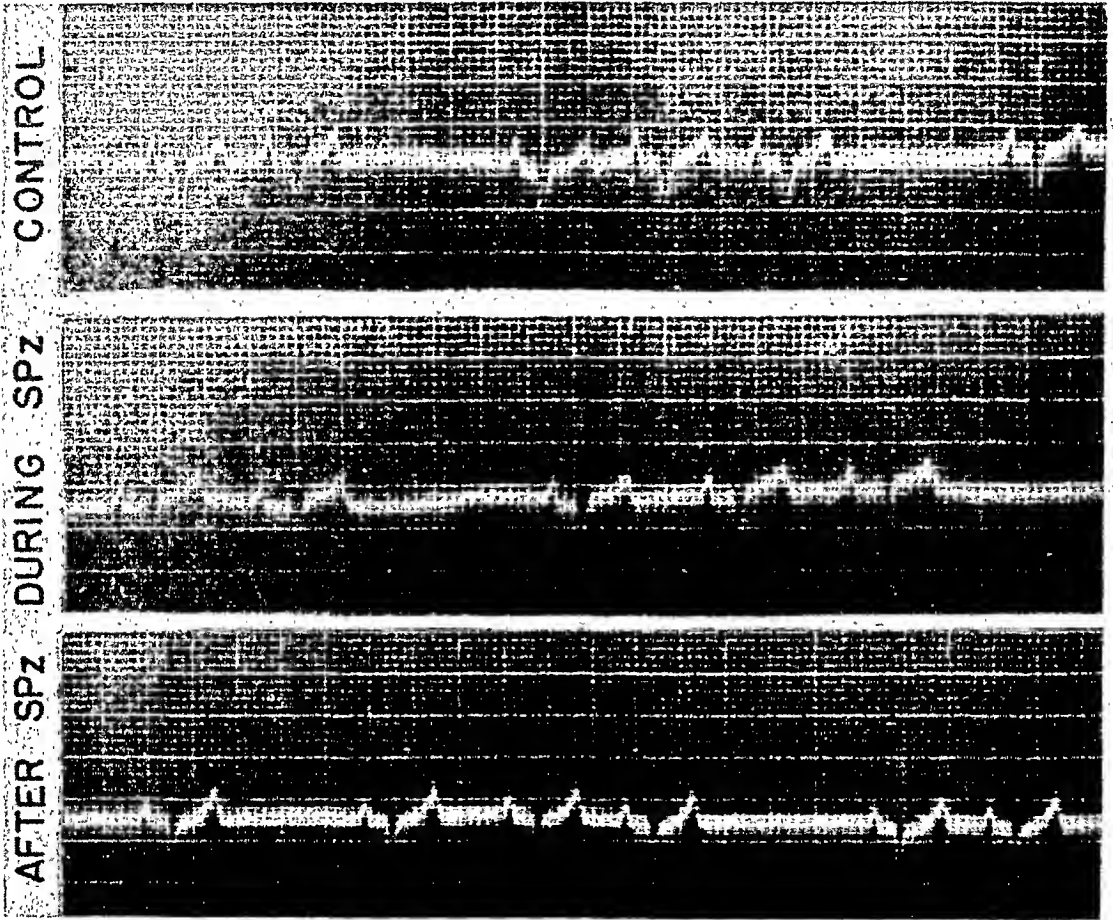


B.

Fig. 2. — (For complete legend see opposite page.)

In the group on heavy dosage, Dogs 14 and 9 showed electrocardiographic changes during medication. Dog 9 died five days after Dose 8, with a drug blood level of 83 mg. per cent twelve hours before death. Its control electrocardiogram showed a prolonged conduction time (.132 second; rate, 112 per minute) which was not affected by the drug, but the S-T segment was depressed and the T wave became diphasic. These changes did not appear until after Dose 5 in the second course, when the blood drug level had started to rise (111 mg. per cent after Dose 8) and persisted until death (Fig. 3, B). Drug elimination was slow.

Dog 14, which survived the full sixteen doses of the drug, had a diphasic T wave in the control. This became positive and increased in amplitude during drug administration but returned to the control pattern after the drug was withdrawn. Drug elimination was so slow that the blood level did not return to normal during the rest periods. Thus the drug accumulated in the blood with each new course and after Dose 16 reached the very high level of 112 mg. per cent. It was still 48 mg. per cent at the end of the usual ten-day observation



A.

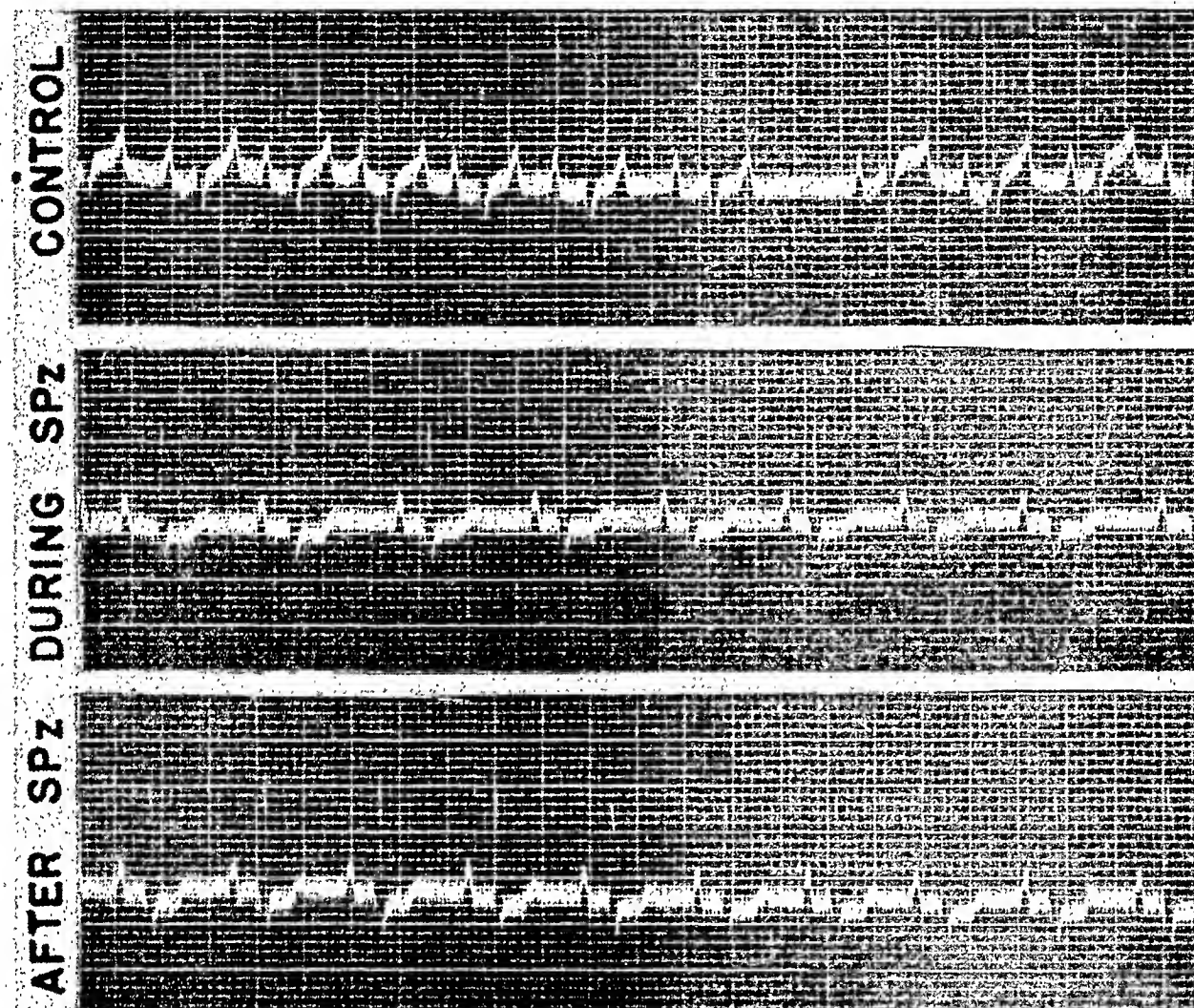
Fig. 3.—Effect of sulfapyrazine. A, Three tracings of Lead II from Dog 27 with a "normal" electrocardiogram showing the sinus arrhythmia often found in the dog. Four courses of sulfapyrazine had no effect on the electrocardiogram and the rhythmicity was unchanged.

B, Three tracings of Lead II from Dog 9. After two courses of sulfapyrazine, the S-T segment shifted downward. This change persisted throughout the remainder of the experiment.

period and 43 mg. per cent eight days later, at which time the heart rate was 56. In spite of the persistence of the high blood level, the electrocardiogram had returned to "normal." The remaining five dogs on heavy dosage showed no electrocardiographic changes, although the toxic effects of the drug were so severe that three died during drug administration and in two instances the drug

was discontinued before completing the full course of sixteen doses (Table II). A marked depression of rate occurred in all dogs during drug administration which persisted after medication.

There were no abnormalities in the control electrocardiograms of the four dogs on the lighter dose. Dog 24 showed a transient depression of the S-T segment and a change in direction of the T wave during medication. In some of



B.

Fig. 3.—(For complete legend see opposite page.)

these tracings, there seemed to be a slight increase in conduction time which was also present after the drug was withdrawn. Dog 25 also showed S-T segment depression and a diphasic T wave in most tracings during drug administration; both of these electrocardiographic changes persisted. No changes occurred in the other dogs throughout the experiment (Fig. 3, 4). No significant rate changes occurred in any of this group. The lighter dose was well eliminated during the rest periods and the drug was gone from the blood before the next course was begun (Table II), thus preventing cumulative effects during the experiment.

Some toxic effects were present, however, during drug administration, and the animals showed a slight weight loss due to vomiting and anorexia while the blood level was high.

DISCUSSION

The high incidence of deviation from the "normal" electrocardiogram in these apparently healthy dogs emphasizes the need for well-established control observations on dogs, especially in any study involving the cardiovascular system, in order to avoid the danger of erroneously attributing such changes to the experiment. A recent study by Morehead and Little¹⁴ further emphasized this need. They reported blood vessel changes in twenty-eight "healthy" mongrel dogs showing a high incidence of extensive vascular changes in all age groups, even puppies. Thirty-five per cent of our animals, which were carefully chosen to be in a young adult group and healthy as far as physical examination could determine, showed abnormalities in conduction.

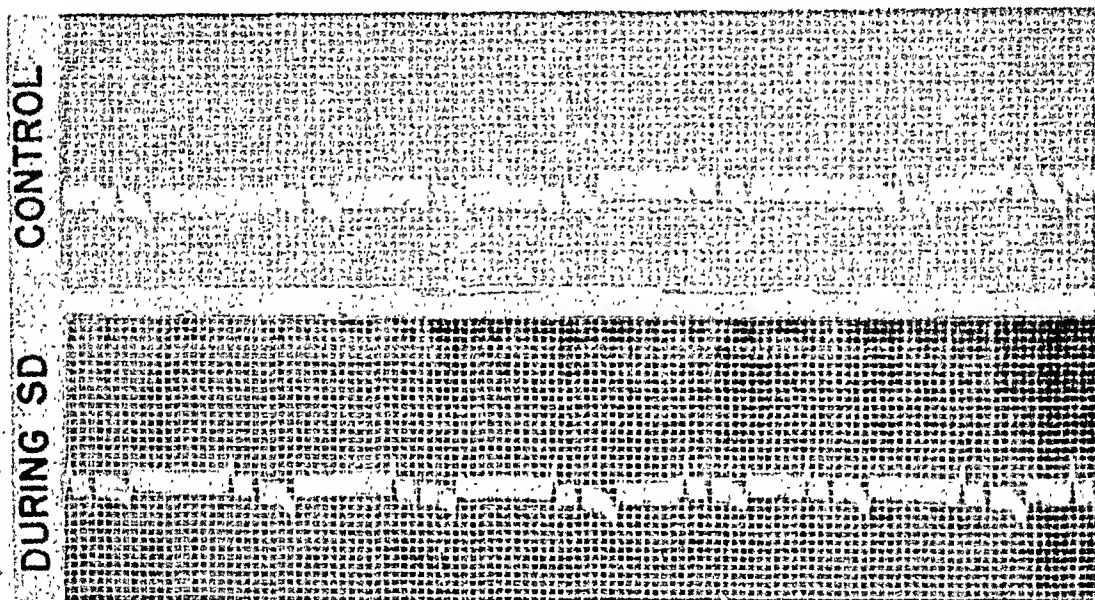


Fig. 4.—Effect of sulfadiazine. Two tracings of Lead II from Dog 7 with "normal" electrocardiogram. No change occurred in the electrocardiogram during medication, although drug toxicity caused death after the first course of injections.

The absence of electrocardiographic changes in thirty-two of the thirty-nine dogs studied in this series is in accord with the experimental findings in other studies which have indicated that cardiac involvement is not a frequent side effect of chemotherapy. In spite of toxic reactions which were fatal in six cases, the conducting system as such was unaffected by the sulfonamides used (Fig. 4.) Even in the dogs with definite conduction defects in the controls, as shown by A-V block (Fig. 2), the drug did not further depress conduction, and the frequency of dropped beats was unchanged. The duration of the QRS interval remained

remarkably constant in each series (Fig. 1). This does not support Dozzi's⁷ contention that the sulfonamides are "not apt to alter the rhythm unless there is some pre-existing irritability of the conduction system." It is difficult to evaluate his evidence of sulfonamide effects on cardiac function, namely, A-V nodal rhythm, since the electrocardiogram presented for comparison is obviously not normal and the patient gave a history of previous attacks of paroxysmal tachycardia which were probably also of A-V nodal origin. Rhythmicity was not significantly altered by the drug, and rhythm characteristics, such as the marked sinus arrhythmia in Dog 27 (Fig. 3), were unchanged throughout the experiment. P-R interval changes showed the usual correlation with rate changes (Fig. 1). We feel that the rate variations during medication were the result of systemic effects associated with toxicity such as variations in body temperature. This might explain the increased rate noted in the sulfapyridine group since hyperpyrexia has been frequently reported as a side effect with this drug. Unfortunately, daily body temperatures were not determined during these experiments but are now being recorded in subsequent studies.

Cardiac function was, however, affected in seven of the dogs as shown by changes in the electrocardiogram. S-T segment deviation and change in the direction of the T wave were transient in five of the animals but persisted after medication in only two, while prolonged conduction time persisted in one. Electrocardiographic changes of this nature indicate some change in the myocardium which alters its physiologic state. The morphologic changes in cardiac muscle found at autopsy on sulfonamide-treated patients^{3,5} might be expected to give rise to such electrocardiographic effects. The absence of these changes in spite of the frequency of toxic reactions (in 82 per cent of the series) brings up the question of drug idiosyncrasy. The ability of the sulfonamides to act as sensitizing antigens and thus produce hypersensitivity reactions has been emphasized by Rich.⁶ He feels that they thus resemble foreign serum and are responsible for vascular lesions of the periarteritis nodosa type, which may involve the heart. Evidence of cardiac function changes during hypersensitivity reactions has been presented by Fox and Messeloff¹⁵ in a report of transient electrocardiographic effects (S-T segment deviation and amplitude depression) in a boy suffering from serum sickness after tetanus antitoxin. None of the changes which we observed in these animals occurred during the first course of the drug but made their appearance in the later courses after the first rest interval of ten days. Sensitization may well have occurred during this interval in these animals and the subsequent courses of treatment resulted in morphologic changes which gave rise to the electrocardiographic effects. This could only be proved by microscopic study since, at autopsy, careful examination failed to reveal any gross changes in the hearts and blood vessels even in the animals dying during medication.

The extensive use of the sulfonamides prophylactically as well as for minor infections affords an opportunity for widespread sensitization. The frequency of drug hypersensitivity reactions reported in the literature and the histologic evidence of the relationship of such reactions to cardiac and vascular lesions of

varying severity emphasizes the danger of producing such changes if chemotherapy is continued in the face of a hypersensitivity reaction. The possibility of impairment of cardiac function in the gravely ill patient is obvious. Electrocardiographic studies during treatment would give early evidence of cardiac involvement and further indication for stopping the drug to prevent permanent damage; Rich⁶ has suggested that, as the hypersensitivity reaction is of the anaphylactic type, prompt withdrawal of the inciting antigen will halt the progress of the lesions. With this in mind, patients treated with sulfonamides are being followed electrocardiographically and will constitute a future report.

As a result of our observations on cardiac function during sulfonamide therapy, we would like to endorse French and Weller's³ suggestion that cardiovascular function be frequently checked when patients are being given sulfonamides and that electrocardiographic studies might well parallel the course of treatment.

SUMMARY

The effect of various sulfonamide drugs on the electrocardiogram was studied in thirty-nine dogs.

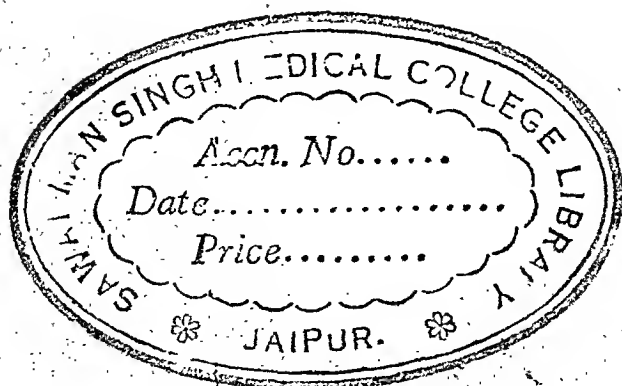
Sulfonamide administration had no effect upon the cardiac muscle and conducting system which could be demonstrated by the electrocardiogram in thirty-two dogs (82 per cent of the number studied), even though eleven of these dogs showed conduction defects before treatment.

Electrocardiographic abnormalities consisting of slight S-T segment deviation and change in direction of T wave occurred in seven dogs during medication and indicated some myocardial involvement. These changes were transient and disappeared after drug administration was stopped in all except three cases. The possibility that these electrocardiographic changes were the result of morphologic changes in cardiac muscle caused by sulfonamide sensitization is discussed.

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Clinical Reports

EFFECT ON THE HEART OF AN OVERDOSE OF EPINEPHRINE

REPORT OF A CASE

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THE effect of epinephrine on the heart and coronary arteries is still a controversial subject. Available literature reveals no case report wherein an overdose of epinephrine produced prolonged electrocardiographic evidence of myocardial injury. For these reasons it is considered worth while to report the following case.

CASE REPORT

C. W. C., a naval aviator, 29 years of age, gave a history of a recent recurrence of malaria. In an attempt to produce a smear of blood which would exhibit malarial parasites, an injection of 0.5 c.c. of a 1:1000 solution of epinephrine hydrochloride was ordered. At 10:15 A.M. on April 11, 1945, an intramuscular injection of 5.0 c.c. of a 1:1000 aqueous solution of epinephrine hydrochloride was given inadvertently. The patient immediately experienced a sensation of constriction in his throat, a feeling of fullness in his chest, precordial distress, and a severe headache. When seen one minute later by the medical officer, he was pallid and in acute distress. His radial pulse was almost imperceptible and the heart sounds were extremely rapid and irregular. Five minutes after the injection, his blood pressure was 120/80. After being in extreme discomfort for about ten minutes, he vomited and felt relieved. In thirty minutes his pulse rate was 140 per minute and regular. At the same time his blood pressure was 160/96. Six hours later his pulse rate was 102 per minute and he felt much better except for a severe headache.

Twenty-three hours after the injection he was admitted to a United States Naval Hospital complaining of a constricting pain in the low parasternal area, some dyspnea, and a left temporal headache. The physical examination revealed a temperature of 101°F.; pulse rate, 105 per minute; respiratory rate, 24 per minute; and blood pressure, 94/60. No abnormal cardiac signs were noted. Breath sounds were decreased over the lower portion of the left lung. X-ray films of the chest revealed increased parenchymal density adjacent to the right and left borders of the heart. The leucocyte count was 8,000.

On April 12, 1945, the day of admission, an electrocardiogram revealed an inverted T wave in Lead I, a sharply inverted P wave in chest leads CF₂ and CF₄, and a 2 mm. elevation of the S-T segment in Lead CF₂. The following day the T wave in Lead I was more deeply inverted and the T wave in Leads II and III were of greater amplitude. On April 27, the inversion of the T wave was less and there was no elevation of the S-T segment. By May 16 the T wave in Lead I

Statements made in this article are those of the authors and do not necessarily represent the views of the Navy Department.

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was diphasic and by June 9 (fifty-nine days after the injection of epinephrine) the electrocardiogram was within normal limits, with upright T waves in Lead I and upright P waves in the chest lead.

Clinically the patient improved rapidly. His temperature was normal the day after admission. By April 16 all chest symptoms had disappeared and on April 18 an x-ray film of the chest was normal. The erythrocyte sedimentation rate was 22 mm. per hour on April 17 and 17 mm. per hour on May 7. By May 8 the left temporal headache, the most persistent and last symptom, was gone and he was allowed to be out of bed. Further convalescence was uneventful.

COMMENT

After reviewing the recent literature, Levy¹ stated that there was still a difference of opinion regarding the action of epinephrine on the coronary arteries. Studies of the effect of suspending short sections of a coronary artery in a solution of epinephrine gave a diversity of reactions. Studies on the rate of coronary circulation in the intact heart and in the perfused heart showed a decrease in the rate of perfusion after small doses of epinephrine but increased cardiac activity and an increased perfusion rate after larger doses. Other observers reported that epinephrine caused an increase in cardiac rate and a decrease in the coronary flow. Epinephrine applied directly to the coronary arteries of the tortoise produced constriction of the vessels.

Sollman² stated that the constrictor effect of epinephrine was weak in the coronary arteries and that in the intact animal these vessels were passively dilated by the displacement of blood from the more powerfully constricted areas. Subsequently, he stated that clinically epinephrine probably caused coronary constriction and in most cases reduced the flow of blood through these arteries.

Levy¹ reported what many have confirmed: that 1.0 c.c. of a 1:1000 solution of epinephrine hydrochloride injected subcutaneously into a patient who has had angina pectoris will produce a typical attack of pain. This seemed to be evidence that epinephrine reduced the flow of blood through the coronary arteries.

Katz³ listed epinephrine as a drug which may cause extrasystoles, depression of the S-T segment, and inversion or flattening of the T waves. He reproduced electrocardiograms from a case of angina pectoris which showed depression of the S-T segment in Leads I and II and a moderate flattening of the T wave in Lead I, sixteen minutes after the injection of 1.0 c.c. of a 1:1000 solution of epinephrine hydrochloride.

It has been stated by Katz³ and Sigler⁴ and in *The Epitome of the Pharmacopeia of the United States*⁵ that toxic doses of epinephrine caused ventricular fibrillation.

SUMMARY

A naval aviator was inadvertently given an injection of 5.0 c.c. of a 1:1000 solution of epinephrine hydrochloride. The arrhythmia noted in the first thirty minutes could have been due to frequent extrasystoles or to transient ventricular fibrillation. The precordial distress, the transient elevation of tem-

CF₂.CF₄CF₂CF₄

Fig. 1.—The first tracing was made twenty-three hours after the hypodermic injection of 5.0 c.c. of a 1:1000 solution of epinephrine hydrochloride. The last tracing was made fifty-six days after the drug was received.

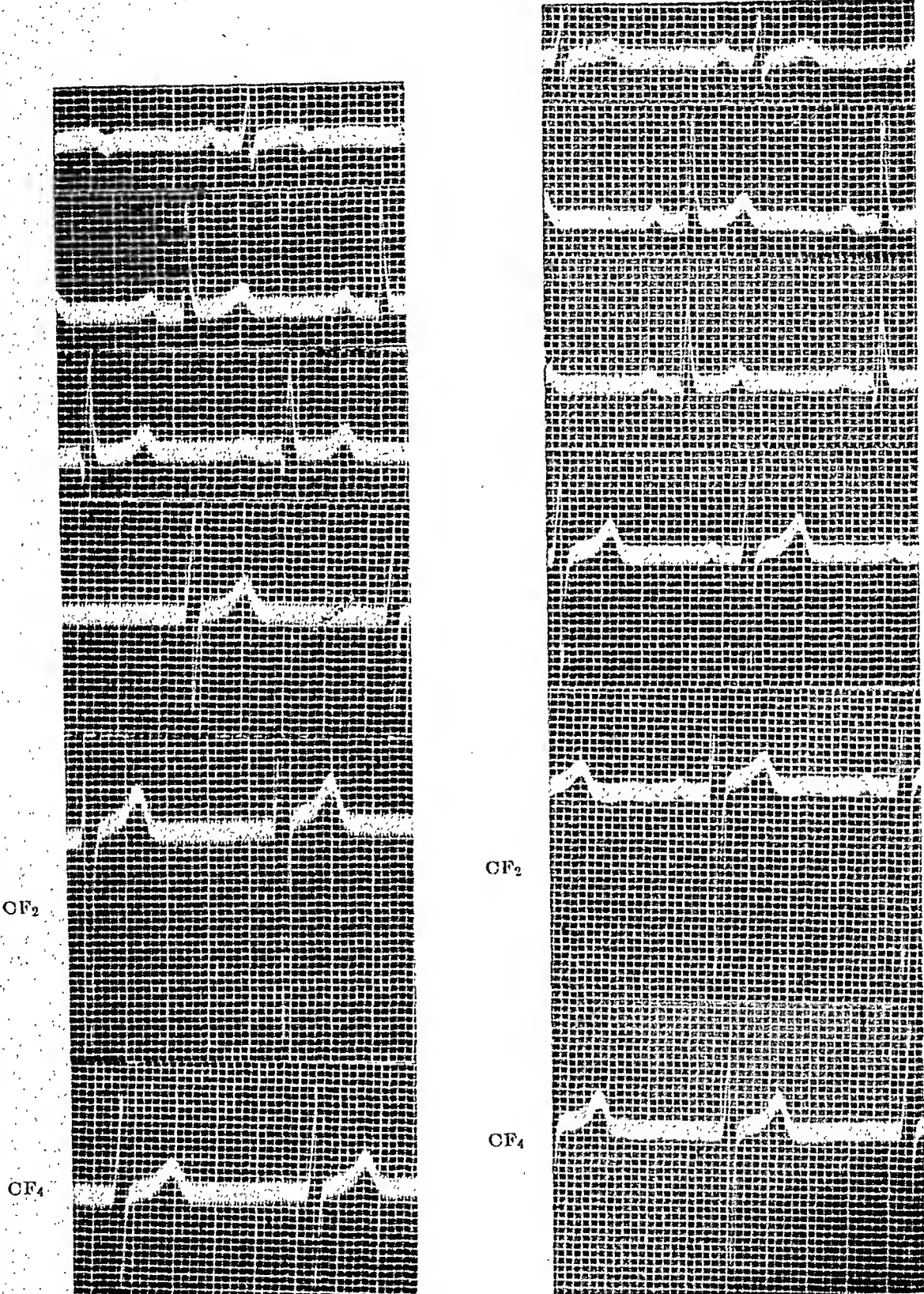


Fig. 1 Cont'd.—(For complete legend see opposite page.)

perature, the increase of sedimentation rate, and the prolonged electrocardiographic changes could have been due to actual infarction of the myocardium. The evidence in this case indicates that epinephrine in large doses causes relative coronary insufficiency in the normal adult.

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A CASE OF LARGE OVERDOSE OF EPINEPHRINE

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RECENTLY I had the unfortunate experience of observing a patient suffering from urticaria who was given 7.0 c. c. of a 1:1000 solution of epinephrine. The physician in charge had ordered 7 minims and an apprentice, who mistook the order, administered 7 c. c. intramuscularly in the right buttock. Fig. 1 shows the result, which fortunately was not particularly dramatic. The error was dis-

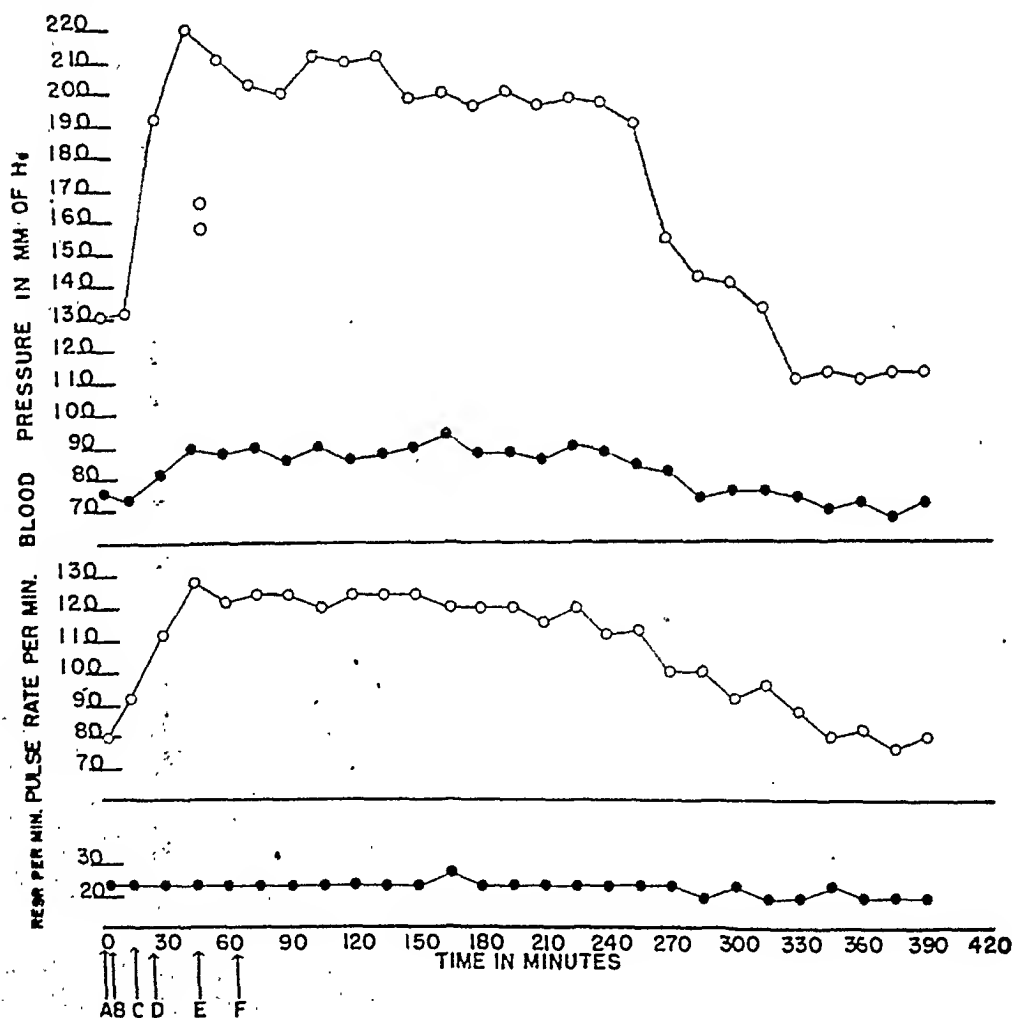


Fig. 1.—A, Administration of 7.0 c.c. 1:1000 solution of epinephrine intramuscularly in the right buttock. B, 0.4 Gm. sodium amytal administered by mouth. C, Patient put to bed with head elevated. D, Ice pack applied to site of injection with minimum of pressure. E, Patient developed mild headache. F, Patient given 0.6 Gm. aspirin and 0.03 Gm. codeine sulfate.

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covered immediately by a supervisor when the apprentice returned from the patient's room with a 10 c. c. syringe, attached to which was a No. 20 needle used commonly for intramuscular injections. The patient, a healthy adult male, 21 years of age, was treated, as shown in Fig. 1, by bed rest, sodium amytal, an ice pack applied to the site of injection with as little pressure as possible, and elevation of the head. He was completely undisturbed and unable to understand why he was being treated at all or why the blood pressure was being taken regularly at fifteen-minute intervals. His only symptom was a slight headache, for which he was given 0.6 Gm. of aspirin and 0.03 Gm. of codeine sulfate. There was no excessive perspiration and no cardiac arrhythmia observed at any time other than the mild degree of tachycardia noted in Fig. 1, of which the patient was barely conscious.* He did develop mild tremor. The highest blood pressure recorded at any time was 220/96. The pulse rate reached 128 per minute. The respiratory rate varied between 20 and 28 per minute. At the end of five hours blood pressure, pulse, and respiration had all returned to normal.

It was thought that the epinephrine must have caused considerable angiospasm at the site of injection, thereby allowing itself to be absorbed slowly by the systemic circulation over the five hours' time.

Two months later the patient was observed to have no apparent ill effects from his ordeal.

Incidentally, the dosage given ameliorated the urticarial condition.

SUMMARY

Seven cubic centimeters of a 1:1000 solution of epinephrine were administered to a patient intramuscularly in one dose. He had no immediate effects of a really violent nature and no permanent effects.

*It is unfortunate that the electrocardiograms which were made are no longer available. These tracings were carefully studied by competent physicians who could find in the tracings nothing except a moderate simple tachycardia and possibly a slight change (less than 1.0 mm.) in the height of the T waves.

CONGENITAL COMPLETE HEART BLOCK DIAGNOSED IN UTERO WITH SOUND TRACINGS AND SIMULTANEOUS ELECTROCARDIOGRAPH OF THE MOTHER

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THE infant was born of a primipara mother who was 33 years of age and in robust health. Five weeks before term it was noticed that the fetal heart sounds were extremely slow; they were counted at 40 to 46 per minute. It was thought that the life of the fetus was in danger, but after observation for several hours with no change in the heart rate no attempt was made to induce labor. During the subsequent ten days the fetal heart rate was always between 40 and 46 per minute. Sound tracings of the fetal heart was made simultaneously with the maternal electrocardiogram and are presented in Fig. 1.

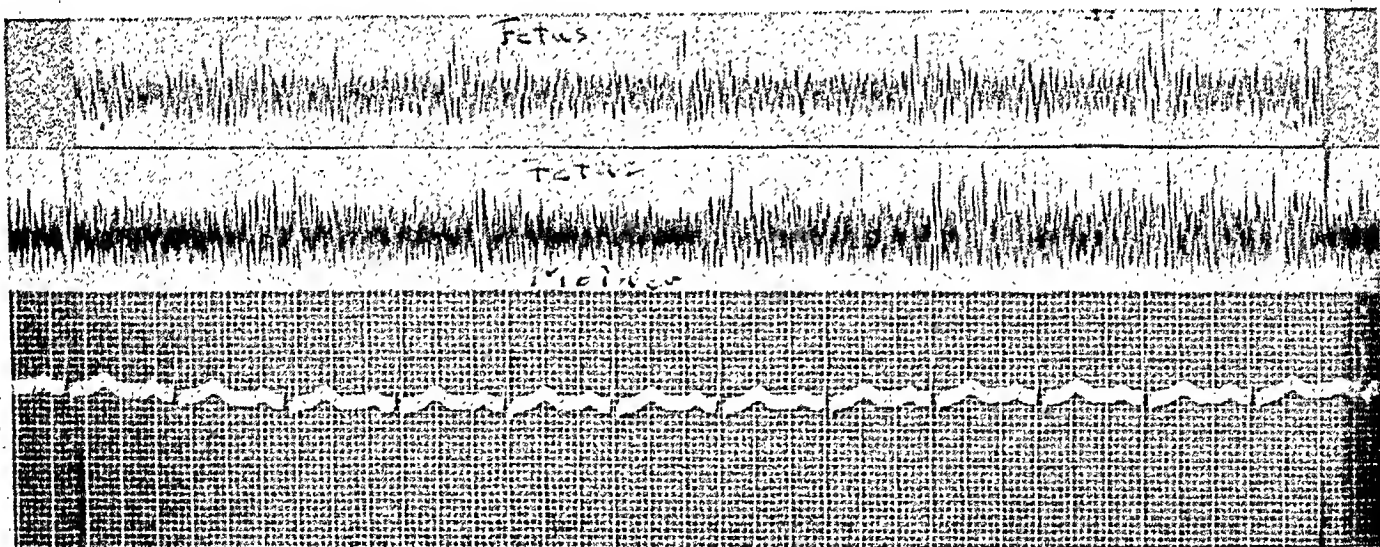


Fig. 1.—Sept. 11, 1944. A, Fetal heart sounds alone; rate, 48. B, Fetal heart sounds recorded synchronously with maternal electrocardiogram. The fetal heart rate was 48 per minute; the maternal heart rate, 95 per minute.

The mother was delivered at the beginning of the ninth month. The baby was an apparently healthy infant weighing 5 pounds, 12 ounces. Sound and electrocardiographic tracings made after delivery are shown in Fig. 2.

Since birth, the infant has presented a difficult feeding problem. Regurgitation of food is still frequent, yet fairly normal growth has taken place. At

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†Fred C. Jordan, M.D., died July 29, 1945.

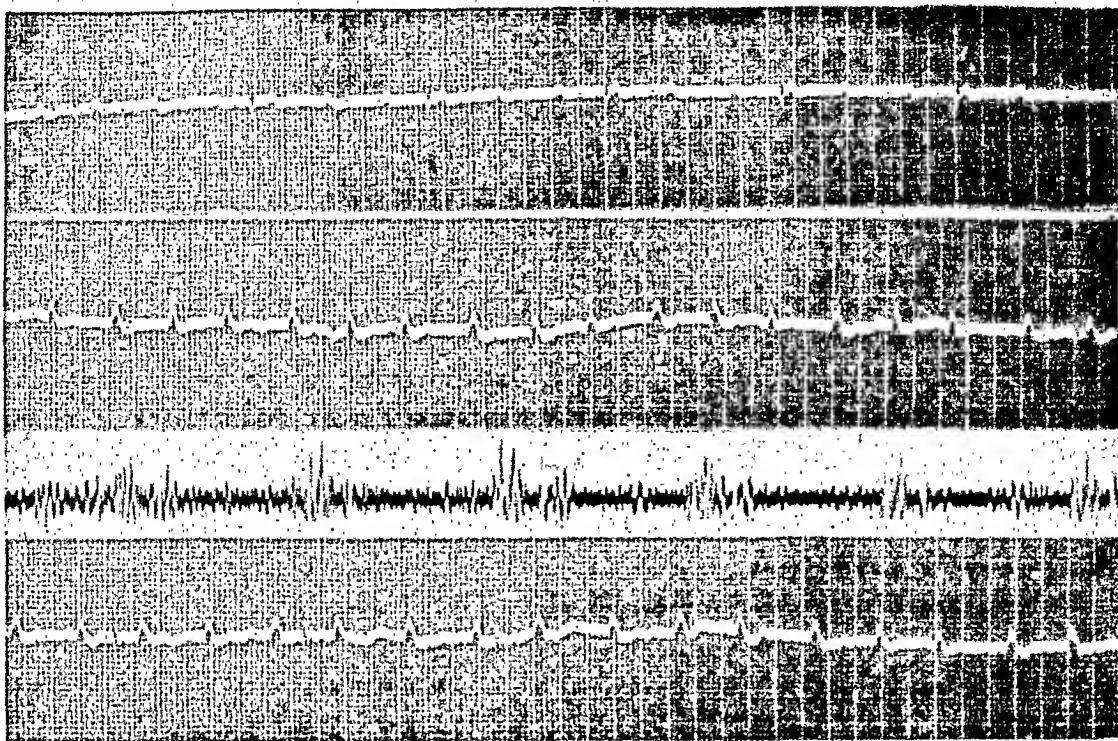


Fig. 2.—Sept. 14, 1944. Infant electrocardiogram and infant phonocardiogram recorded synchronously. Ventricular rate is 43 per minute; auricular rate, 124 per minute.

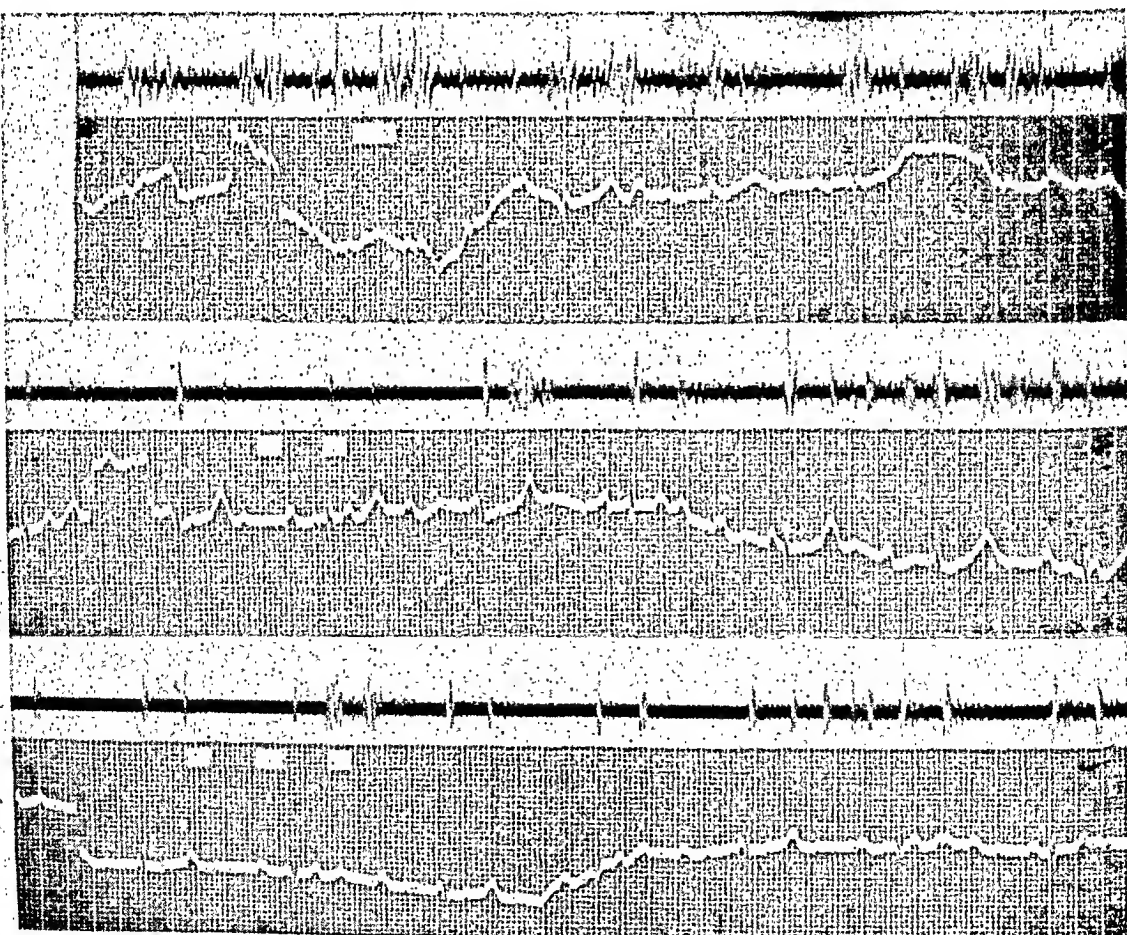


Fig. 3.—Sept. 4, 1945. It was technically difficult to take this tracing because of the constant movement of the infant. It shows complete heart block with disassociation of auricular and ventricular contraction. The graph remained about the same as that shown on the tracing taken at 2 days of age. The ventricular rate is 44 per minute; auricular rate, 130 per minute.

12 months of age the weight was $17\frac{1}{2}$ pounds and the length, 29 inches. The lips were pale, the tissues somewhat flabby, and the skin rather loose. Eight teeth were present. There was no lymphadenopathy and the lungs were clear. There was a short definite systolic murmur audible at the apex and at the left third interspace. The second sound was distant and normal. These findings are recorded on the various phonocardiograph tracings, even on the tracing of the fetus taken in utero. The liver was not enlarged, the spleen was not palpable, and the extremities were normal. An electrocardiogram and a phonocardiogram made at the age of 12 months are shown in Fig. 3.

ARTERIOSCLEROTIC ANEURYSM OF THE CARDIAC CORONARY ARTERIES

REPORT OF A CASE

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DESPITE the frequency and severity of involvement of the coronary arteries by atherosclerosis, true aneurysm formation resulting from this type of purely degenerative process is rare. The most recent comprehensive collection of cases of coronary artery aneurysms due to all causes is that of Packard and Wechsler.¹ Of thirty aneurysms discussed by them, seven were classified as "mycotic-embolic," while twelve were considered to be definitely arteriosclerotic. In the remaining eleven cases insufficient data were presented to permit of their accurate classification.

Since the report of Packard and Wechsler, additional single cases of atherosclerotic aneurysms have been presented by Eliasoph,¹⁰ Cox and Christie,¹¹ Chiari,¹² Nagayo and Takahashi,¹⁴ and Domenichini.¹⁵ It is the purpose of this presentation to analyze the anatomic details of the aneurysms previously reported and to add an additional case.

REPORT OF CASE

The patient was a 42-year-old thin, spare, high-strung man. He was the proprietor of a music store and had been in good health until about five years before his last illness when he visited his physician for some minor complaint. A complete physical examination at that time revealed no evidence of hypertension or diabetes. He had felt perfectly well until his present illness.

About two weeks before his death he began to notice slight dyspnea and precordial distress after exercise. The final fatal illness was ushered in with the sudden onset of severe precordial pain radiating to the left arm, associated with "a heavy feeling on my chest, as if a sand bag had been placed there." The patient went rapidly into shock and expired about twenty-four hours later.

Autopsy was performed three hours after death. With the exception of marked pulmonary edema and congestion of the abdominal viscera, the pertinent findings were limited to the heart and the aorta.

The heart was slightly enlarged, weighing 380 grams. It measured 15 cm. from base to apex and 13 cm. in its widest diameter. A small partially organized fibrous tag bound the apex to the parietal pericardium. The epicardium showed moderate focal congestion which was especially prominent over the anterior longitudinal sulcus. On section of the left ventricular myocardium, a large, soft, well-demarcated red zone of discoloration was seen in the posterior two-thirds of the lateral wall. It measured 4 by 7 cm. in size. A similar but smaller focus of discolored myo-

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cardium 3.1 by 2.5 cm. in size was present in the interventricular septum. The papillary muscles of the left ventricle presented some yellow opaque foci of infarction most prominent at their apices. The cardiac valves showed no abnormalities.

After dissection of the epicardial fat, the coronary arteries were exposed, and the unusual changes about to be described were disclosed. The left coronary artery arose from its usual site and measured 1.2 cm. in length. The anterior descending branch, as well as the main artery itself, showed extensive intimal plaque formation and moderate dilatation of the lumen. The circumflex branch was markedly sclerosed and the lumen, just distal to its point of origin, was narrowed to a pin-point opening by concentrically arranged yellow atheromatous plaques. At a point 1 cm. from the origin of this branch a large fusiform aneurysm measuring 2.4 cm. in length and 1.2 cm. in width was present (Fig. 2). The lumen of the vessel at the site of aneurysm formation was patent, and no mural thrombus was seen.



Fig. 1.—Saccular aneurysm of the right coronary artery, just distal to its first bifurcation. The sub-epicardial fat has been partially dissected.

The right coronary artery pursued a normal course in the right atrioventricular groove for a distance of 2.9 centimeters. At that point, just after the origin of a small vessel which supplied the apex of the right ventricle, a saccular aneurysm measuring 1.2 by 1.2 by 1.1 cm. was present (Fig. 1). The outer wall of the aneurysmal sac was markedly sclerotic and of a bright yellow color. The continuation of the right coronary artery beyond the aneurysm showed extensive intimal sclerosis with superimposed calcification and almost complete obliteration of the lumen.

Longitudinal section through the aneurysm of the right coronary artery revealed a saccular structure which was covered externally by slightly thickened adventitia (Fig. 3). The media had apparently been completely destroyed at the summit of the sac and the remainder of the aneurysm wall was composed of the bright yellow opaque atheromatous intima which showed foci of hemorrhage. Attached to the inner lining of the sac was a large grayish-brown thrombus which was spongy, granular, and translucent. The lumen of the vessel at this point appeared as a thin slit beneath the thrombus.

Microscopic examination of the heart revealed three foci of early infarction characterized by necrosis of the myocardial fibers, neutrophilic infiltration, and surrounding congestion. Moderate infiltration of the epicardial fat by neutrophiles was also present.



Fig. 2.—The right coronary artery and aneurysm are shown above. Below and to the left is a transverse section through the distal portion of the right coronary artery, showing almost complete occlusion of the vessel. Below and to the right is shown the fusiform aneurysm of the circumflex branch of the left coronary artery.

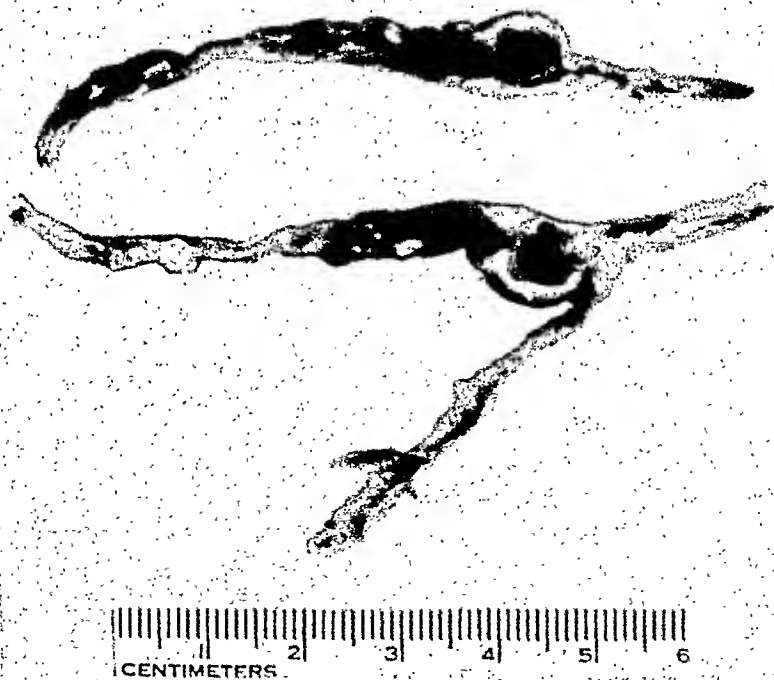


Fig. 3.—Longitudinal section through the sacular aneurysm showing the advanced atherosclerotic lesion in its wall and a large mural thrombus. Note the extensive atherosclerotic change in the remainder of the artery.

The coronary arteries were the seat of extremely advanced atherosclerosis. Large deposits of lipid material and calcium salts in many places almost obliterated the lumens of the arteries. Where the intimal plaques were most extensive, the underlying media was markedly thinned out. Sections through the wall of the saccular aneurysm revealed that at its widest portion the sac was covered externally by only a thin layer of fibrotic adventitia. The collagenous fibers of the adventitia in this section showed moderate hyalinization. Beneath the thin rim of adventitia the media had been completely destroyed and the thickened intima showed a wide zone of infiltration by lipid material and calcium salts. Focal collections of inflammatory cells, most of which were lymphocytes and plasma cells, were present adjacent to the accumulation of lipid material. Many foreign body giant cells were noted, some containing as many as sixty nuclei. The cytoplasm of some of the giant cells contained rounded globules and cleftlike deposits of lipid in addition to a few granules of light yellow-brown pigment which was probably hemosiderin. The brown pigment was also seen in the cytoplasm of isolated macrophages as well as extracellularly. A large, partially organized, recanalized mural thrombus occupied the largest part of the aneurysmal sac. The newly formed vascular channels were lined by markedly hyperplastic endothelial cells. In some places remnants of deeply eosinophilic fibrin were seen. Beneath the thrombus was a small slitlike lumen which was lined by endothelial cells. Where the aneurysm took origin from the vessel wall, remnants of atrophic and compressed muscle fibers of the media were still visible.

Sections of two bifurcations of the right coronary artery showed no defects in the muscularis. Preparations stained to show elastic tissue revealed no abnormalities of the inner elastic membrane in the grossly uninvolved portions of the coronary arteries. However, there was total destruction of this membrane in those branches of the right coronary artery where the atheromatous plaques were most prominent. No elastic fibrils could be found in the wall of the aneurysm.

The ascending aorta showed extensive atheromatous change. Many irregular, slightly raised, moderately indurated, broad, yellow plaques were present in its intimal coat. The plaques were present throughout the ascending aorta, extending proximally as far as the sinuses of Valsalva, where they surrounded both coronary ostia and produced partial stenosis of the right ostium (Fig. 4). The latter measured 0.2 cm. in diameter, whereas that on the left measured 0.5 centi-



Fig. 4.—Extensive intimal atherosclerosis of the ascending aorta, with involvement of the sinuses of Valsalva and partial stenosis of the ostium of the right coronary artery. These plaques were bright yellow in color. There is conspicuous absence of intimal wrinkling and stellate scars.

eters. The wall of the aorta showed no pearly-white plaques, intimal wrinkling, or thickening of the adventitia, changes such as are found in syphilitic aortitis.

Microscopically, the aorta showed marked intimal thickening and many foci of hyalinized collagen. Large deposits of lipid material, lipophages, fibroblasts, and focal areas of calcification were also noted. The media contained many focal collections of lymphocytes and in one situation neutrophils were present. The adventitial fat was moderately and relatively diffusely infiltrated by lymphocytes.

The final anatomic diagnoses were as follows: aneurysms, saccular and fusiform, multiple, atherosclerotic, of coronary arteries; stenosis, partial, of right coronary ostium by atherosclerotic plaque; infarct, recent, of left ventricular myocardium and interventricular septum; atherosclerosis, marked, of aorta and coronary and pulmonary arteries; pericarditis, acute, slight; edema, moderate, of lungs; congestion, marked, of liver, spleen, and kidneys; necrosis, acute, focal, of liver; fibroma of left renal medulla; hemorrhages, recent, mucosal, of renal pelvis.

COMMENT

Packard and Wechsler listed twelve cases of coronary artery aneurysms as definitely of arteriosclerotic origin but objection may be raised to the inclusion of the cases of Wood¹⁷ and Martland¹⁸ and to the exclusion of Toller's¹¹ case, which was classified by them as probably mycotic-embolic. Concerning the last case, they state that "unfortunately the condition of the heart valves is not mentioned," but reference to Toller's paper reveals that "the aortic valve contained dense masses of calcareous material, but there were no vegetations." The aorta showed extensive atheromatous change, and the right coronary artery "was diseased from end to end." The left coronary artery distal to the aneurysm was normal. In the absence of histologic examination of the wall of this aneurysm, no definite etiology can be said to be established, but from the evidence at hand it is probable that the case belongs in the group due to atherosclerosis.

In a discussion of a case presented by Clark before the New York Pathological Society, Wood¹⁷ stated that he "presented to the society some years ago an aneurism of the coronary artery . . .," but no formal reference to a published paper could be found. Martland's case was that of a 32-year-old Negro woman who died of cardiac tamponade secondary to a massive hemopericardium. There was an aneurysm of the supra-valvular portion of the aorta measuring 2.5 by 4 by 1.5 centimeters. The pouch and the surrounding aorta for a distance of 4 cm. above the aortic ring showed a rubbery, irregular, but smooth appearance. The intima presented numerous grayish-blue hyaline, slightly raised areas, many of which showed small depressions or distinct puckered scars. In addition, there was a globular aneurysm of the right coronary artery arising immediately beyond the right coronary ostium. Martland concluded that "as regards the etiology of this lesion, we have undoubted gross evidence of a luetic mesoaortitis." While it is true that "early and superimposed atherosclerosis" was present in the aortic aneurysm, no mention was made of any atherosclerotic change in the aneurysm of the right coronary artery.

If the revised interpretation of the listed cases is acceptable, there have been seventeen authentic cases of atherosclerotic aneurysm of the cardiac coronary arteries, including the five published since Packard and Wechsler's paper and the present one. All of these cases are listed in Table I.

TABLE I. FINDINGS IN THE SEVENTEEN REPORTED CASES OF ARTERIOSCLEROTIC ANEURYSMS OF THE CARDIAC CORONARY ARTERIES

AUTHOR	AGE	SEX	CLINICAL HISTORY	SITE	SIZE	RUPTURE	CORONARY ARTERIES	REMARKS
1. Crisp	63	M	Sudden death	R	Walnut	Yes	Moderate atheroma	Atherosclerosis of aorta
2. Peste	77	M	Myocardial infarction	L	Large nut	Yes	Calcification	Rupture of left ventricle
3. Peacock	51	M	Cardiac failure	L	Pigeon's egg	No	Ossification of left, calcification of right	Fibrinopurulent pericarditis
4. Buchner	47	M	Sudden death	L	6 cm.	No	Bony plaques on floor of aneurysm	Fibrinopurulent pericarditis
5. Capps (a)	48	M	Found dead	L	Pigeon's egg	No	Calcification of left, atheromatosis of right	Atheromatosis of aorta
6. Capps (b)	39	M	Convulsions, bronchopneumonia	L	Hazel nut	No	Atheroma and calcification	No mention of proved syphilis
7. Winkler	68	M	L	Small hazel nut	No	Thickening and calcification	Scarring of myocardium
8. Sommer	73	M	L	2 peas	Yes	Slight atheromatosis	Rupture of aneurysm into wall of pulmonary artery
9. Windholz	62	F	Cardiac failure	L	Nut	No	Paper-thin, hyaline deposits	
				L	Pea	No	Rigid walls, calcific plaques	
10. Packard and Wechsler	60	M	Found dead soon after anginal seizure	L	Pea	Yes	Marked atherosclerosis with calcification	Slight myocardial fibrosis
11. Toller	40	M	Cardiac failure	L	Hen's egg	No	Severe sclerosis of right coronary artery	Aortic valves calcified
12. Eliasoph	58	M	Cardiac failure	L	7 mm.	No	Marked atherosclerosis; dissecting aneurysm in wall in region of aneurysm	Ventricular aneurysm secondary to myocardial fibrosis
13. Cox and Christie	65	M	Cardiac failure	R	2.5 cm.	No	Marked atherosclerosis and calcification	Myocardial fibrosis
14. Chiari	34	M	Cardiac failure	R	10 cm.	Yes	Extensive atherosclerosis	Congenital widening of ostium
15. Nagayo and Takahashi	70	M	Cardiac failure	L	7 by 1 by 1.8 cm.	No	Extensive atherosclerosis	Myocardial fibrosis
16. Domenichini	77	M	Pneumonia; no cardiac symptoms	L	Nut	No	Severe atherosclerosis
17. Mitchell	42	M	Myocardial infarction	R	1.2 by 1.2 by 1.1 cm.	No	Advanced atherosclerosis	Stenosis of right coronary ostium by atheromatous plaque of aorta

The single significant predisposing etiologic factor was the predominance of the male sex, all but one of the patients being men. The ages varied from 34 to 77, with a mean age of 57 years. The left coronary artery or its branches were involved in thirteen instances. In four cases the aneurysms were found in the right coronary artery. Multiple aneurysms were described in three cases, while involvement of both right and left coronary arteries was present only in the case herewith reported. The smallest aneurysm was the size of a pea, and the largest approached the size of a hen's egg in greatest diameter. Rupture of the aneurysm had occurred in five cases. Hemopericardium with cardiac tamponade resulted on three occasions. There had been perforation into the myocardium of the right ventricle in one instance and extension to the wall of the pulmonary artery in another.

The cause of death was apparently of cardiac origin in fourteen cases. Of these fourteen; seven deaths were attributed to progressive cardiac failure; two followed typical episodes of coronary thrombosis; two occurred suddenly at varying intervals after anginal seizures; and in two cases the patients were found dead, with no clinical history available. No data about the terminal phase of illness were furnished in one case, but death was presumably of cardiac origin. Of the three noncardiac deaths, two were attributable to pneumonia and one to cerebral hemorrhage.

Of the fourteen deaths of cardiac origin, only five can be traced directly to the aneurysm itself. In three of these instances, the aneurysm had ruptured into the pericardial cavity, and the resultant hemopericardium was the obvious mechanism of sudden death. The remaining two cases showed, respectively, rupture of the aneurysm into the myocardium of the right ventricle and into the wall of the pulmonary artery. The presence of the aneurysm may be considered only as a major contributing factor to the fatal outcome in the latter two cases. In the entire series, therefore, the aneurysm of the coronary artery appeared to be an incidental finding in twelve cases, and the clinical picture was caused either by advanced coronary atherosclerosis and its sequellae, or by extracardiac disease, such as pneumonia or cerebral hemorrhage.

Much work has been done in the past decade or so on the pathogenesis of aneurysms of the cerebral arteries comprising the circle of Willis and its major branches. Forbus¹⁸ first called attention to the constancy of medial muscular defects at the bifurcations of these vessels in patients with so-called congenital or "berry" aneurysms. He found similar defects in the cerebral arteries in those without aneurysms. Forbus also studied the coronary arteries and found that two of nine cases examined showed medial muscular defects at the bifurcations. Glynn¹⁹ later stressed the importance of the elastic layer of the cerebral arteries. By injection experiments, he noted that outpouchings were not formed at the site of artificially produced medial defects if the integrity of the elastica was preserved. Harris,²⁰ in a report of a case of aneurysmal dilatation of the coronary artery associated with a congenital anomaly, studied the elastic tissue of the coronary arteries. He observed deficiency of the elastic tissue of the coronary arteries and attributed the dilatation of the involved vessel to this condition.

In the patient reported on herewith, two bifurcations of the right coronary artery were examined and no medial muscular defects were observed. Elastic tissue stains revealed marked fraying of the elastica at the border of the saccular aneurysm and complete disappearance of elastic fibers within the aneurysmal sac. No defects in elastic tissue were seen in the apparently uninvolved portions of the vessels. These facts, taken together with the location of the aneurysms beyond the points of bifurcation, would tend to eliminate congenital defects as possible factors in the development of the aneurysms. The presence of advanced atherosclerotic changes in the walls of all branches of the coronary arteries as well as in the aneurysmal sac point to an exclusive role for atherosclerosis in the pathogenesis of the aneurysms described.

There is little doubt that the total destruction of the media in the portion of the right coronary artery which was the site of the saccular aneurysm was caused by the slowly enlarging intramural atheroma. Similarly, the aneurysm formation may be attributed to constant intra-arterial pressure exerting its effect on a weakened portion of vessel devoid of elastic fibers. Mural thrombosis and adventitial fibrosis at the summit of the sac only partially explain the absence of rupture in this instance. That the aneurysm did not rupture is probably a fortuitous circumstance and is explained largely by the patient's premature death from myocardial infarction. The infarct in this case was caused by diminished coronary arterial flow occasioned not only by progressive occlusive coronary atherosclerosis, but also by partial stenosis of the right coronary ostium by an aortic atherosclerotic plaque.

The rarity of aneurysms of the cardiac coronary arteries is due in great measure to the strategic nature of the coronary circulation. The frequency of thrombosis as well as hemorrhage into an atheroma with subsequent occlusion with or without thrombosis, together with the fact that coronary occlusion leads so frequently to an early fatal outcome, militate against the development of atherosclerotic aneurysms.

CONCLUSIONS

1. Atherosclerotic aneurysms of the cardiac coronary arteries occur rarely. From the available literature, only sixteen cases have been collected, and one additional case is reported.

2. The strategic nature of the coronary circulation which favors an early fatal outcome from coronary occlusion and myocardial infarction is offered as an explanation for the rarity of coronary artery aneurysms.

3. Aneurysm of a coronary artery is rarely the immediate cause of death. Of the seventeen patients, only five died as a result of rupture of the aneurysm; in the remaining twelve the aneurysm was apparently only an incidental finding.

4. Congenital defects can be eliminated as factors in the development of the atherosclerotic aneurysms of the coronary arteries presented in this paper, since the aneurysms were not located at the bifurcations of the arteries, no medial muscular defects were found, and widespread atherosclerotic changes were present

throughout the coronary arterial circulation as well as in the aneurysmal sacs. The destruction of elastic fibers at the site of atheromas is an important factor leading to aneurysm formation.

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CONGESTIVE HEART FAILURE AND DEATH IN A CASE OF PAROXYSMAL AURICULAR TACHYCARDIA

CASE REPORT

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FROM the time of its first description in 1888 by Bristowe,¹ paroxysmal auricular tachycardia has been known as a slightly disabling, rarely fatal arrhythmia usually occurring in persons with normal hearts. In large series of patients with this disturbance, less than 1 per cent develop congestive heart failure and rarely among these does death occur.^{2,3} It is a common clinical aphorism, therefore, that if heart failure supervenes during an episode of paroxysmal auricular tachycardia, there is underlying organic heart disease.⁴ In the available literature only four cases could be found where death from congestive heart failure during paroxysmal auricular tachycardia occurred, and at autopsy no certain evidence of a previously existing heart disease was found.⁵⁻⁸ In the most clearly described of these cases, the tachycardia had persisted for weeks or months when finally heart failure appeared, and then the hearts showed pathologically cellular infiltrations or recent infarction.

The following case is presented as an example of death from congestive failure shortly after onset of paroxysmal auricular tachycardia in a patient who had presented no clinical evidence of the advanced structural cardiac disease he was found to have at autopsy. The patient had, in fact, undergone a specially devised rigorous medical and physiologic examination before the episode and no abnormality had been detected. This demonstrates that even when no clinical evidence of organic heart disease can be found in persons with paroxysmal tachycardia, the appearance of heart failure shortly after the onset of the tachycardia makes organic disease of the heart a nearly certain diagnosis.

The patient was a 20-year-old private first class whose previous medical and family history were not known beyond the fact that rheumatic fever was denied and there had been no recent severe illness. In May, 1944, four months before onset of illness and after being judged medically sound by his medical officer, he was examined for "fitness for hard work" by examiners at the Harvard University Fatigue Laboratory* who were serving as consultants to the Office of the Quartermaster General of the United States Army in the selection of troops to test military equipment. The physiologic tests consisted of a "step test," in which the subject mounts and descends a two-stepped, twenty-inch platform at the rate of thirty ups and downs per minute to tolerance, and a four-mile forced march with full pack and gun. To both tests the patient's

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*Permission to present this data was generously provided by Dr. Robert C. Sterling, of the Fatigue Laboratory, who supervised the tests.

tolerance was "average": the pulse rate one minute after completing three and one-half minutes of the step test was 160; his elapsed time in the forced march was fifty minutes, forty-five seconds. Following the satisfactory completion of these tests, he was sent to his post where, during the succeeding summer months, he participated as a subject in the testing of rations and wearing apparel in simulated tropical combat conditions.

He had had no prior episode of palpitation and no recent illness when, on the morning of Sept. 6, 1944, after about three hours' walking on a routine thirty-mile hike, he first noted pounding of the heart. No other symptoms were experienced and he determined to finish the hike. Gradually weakness and shortness of breath became prominent and by late afternoon he was obliged to seek relief. He was brought to the camp dispensary by car. The "rapid pulse" was noted and after failure of carotid sinus pressure or gagging to slow it, he was given a sedative and put to bed in the dispensary. He slept fitfully and the next day continued to have a "tachycardia" of uncounted rate. By that afternoon dyspnea and restlessness were becoming marked and he was brought by ambulance to the hospital, a trying three-hour drive.

On admission he was in marked distress but was alert and responsive. He was orthopneic and cyanotic. Pink froth seeped from the corners of the mouth. Blood pressure and temperature were normal. Cardiac examination revealed the apex impulse to be within the mid-clavicular line, a perfectly regular rate of 200 per minute, and no audible murmurs. The lung fields were filled with moist râles and the jugular veins were distended. There was no edema or ascites. An electrocardiogram was immediately obtained which revealed supraventricular tachycardia of a rate of 240 per minute with erect P waves in all leads (Fig. 1).



Fig. 1.—Electrocardiogram made approximately thirty-two hours after the onset of tachycardia. Only Leads II and III are available. The tracing shows a supraventricular tachycardia with a rate of 240 per minute.

Vigorous carotid and ocular pressure were repeatedly applied without success; it was considered unwise to induce vomiting in view of the dyspnea. He was given 10 mg. of morphine sulfate hypodermically with some improvement and he drifted off to sleep. Four hours later, however, he again became dyspneic and the bloody froth reappeared. He was placed in an oxygen tent, a 500 c.c. phlebotomy was performed, intravenous digitalization was begun (0.4 Gm. initially, 0.2 Gm. at two-hour intervals thereafter), and tourniquets were applied to the limbs. Mecholyl and quinidine were not available. The patient never rallied; he died three hours later, or eight hours after admission and about forty hours after onset of the tachycardia.

Autopsy.—All organs and cavities were normal with the exception of the heart and lungs; the brain was not examined. Both lungs showed marked acute passive congestion with filling

of the entire bronchial tree with bloody frothy fluid; there was no evidence of consolidation. The heart weighed 400 grams; there was no significant dilation of chambers or hypertrophy of the myocardium; chordae tendineae and papillary muscles were intact. The mitral valve admitted one finger with difficulty and presented the typical "fishmouth" appearance of advanced mitral stenosis with thickened distorted valve edges mounted with small glistening gray nodules. There was an almost complete underlying band of calcification, and the attached chordae tendineae were moderately thickened. There was slight thickening of the edge of aortic valve cusps without separation of leaflets. The coronary arteries were patent throughout. Microscopic examination of the myocardium showed scattered small areas of fibrosis. No typical Aschoff bodies were seen. Impression: rheumatic fever, chronic, with marked mitral stenosis.

SUMMARY

A case of paroxysmal auricular tachycardia is presented which in a matter of hours led to acute congestive heart failure and terminated fatally. The case is of interest (1) because the patient had been tested rigorously medically and physiologically for work tolerance before the episode and was believed to be normal and (2) because the presence of the marked mitral stenosis could not be demonstrated before death. The diagnosis depended on the clinical aphorism, "paroxysmal auricular tachycardia leads early to heart failure only in the previously diseased heart."

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Abstracts and Reviews

Selected Abstracts

McGowan, J. M.: Cervical Rib: The Role of the Clavicle in Occlusion of the Subclavian Artery. *Ann. Surg.* 124: 71 (July), 1946.

A study is reported of a series of cases of cervical rib in which it was found that a subclavian artery was intermittently occluded by mechanical pressure between the clavicle and the aberrant rib. In one of these cases the vascular disturbances were sufficiently severe to lead to gangrene of three digits of the right hand.

It has been generally believed that symptoms from cervical ribs are produced in many cases by pressure from the scalenus anticus muscle. This was found to be only partly correct by the author. The important structure of counterpressure is the clavicle. Vascular symptoms are produced by occlusion of the subclavian artery between the cervical rib and the clavicle. In the cases reported, the pulse was occluded partially or completely by the clavicle when the position of attention was assumed by the men.

In addition to crowding from a cervical rib and a hypertrophied scalenus anticus muscle, the costoclavicular state may be further narrowed by (1) elevation of the thoracic cage and (2) depression of the shoulder. The first condition is brought about by excessive use of the muscles of extraordinary respiration such as the sternocleidomastoid and the scalene group; and the second, by carrying a pack and by prolonged periods of standing in the position of attention. The longer the cervical rib, the greater the possibility of costoclavicular compression. Ribs 4 cm. or more are liable to be symptomatic. The more laterally placed the tip of the rib is, the more liable it is to produce symptoms. Right-sided cervical ribs produce symptoms four times more often than those on the left.

In three of the nine patients with cervical ribs that were operated upon, partial removal of the cervical rib was performed as well as a scalenotomy. The results in the operated cases were all good.

NAIDE.

Harken, D. E.: Foreign Bodies in and in Relation to the Thoracic Blood Vessels and Heart. *Surg., Gynec. & Obst.* 83: 117 (July), 1946.

The danger of erosion and suppuration attending large retained missiles in relation to thoracic blood vessels is real. Three deaths from massive hemorrhage due to erosion have come to the attention of the author. Approximately 15 per cent of the thoracic vessel foreign bodies in the series presented have been associated with abscess formation, over 30 per cent were associated with other foreign material such as cloth or bone, and 67 per cent showed pathogenic bacteria on culture. It is, therefore, the author's policy to remove all foreign bodies measuring 1 or more centimeters in two dimensions. The technical difficulty of finding such fragments with operation are insignificant. In only one instance was there failure to remove a fragment.

Seventy-eight foreign bodies have been removed from within, or in relation to, the thoracic great vessels. Three of these were embolic. One of the three embolic bodies lodged in the left

pulmonary artery, another travelled from the heart to lodge in the innominate artery, and the third shifted from the left to the right pulmonary artery. All of these were removed without incident and with restoration of vascular continuity. Another series of fifty-six foreign bodies that have been removed from within or close to the heart is discussed. Thirteen of these were removed from the chambers of the heart. Indications for the removal of foreign bodies in great vessels and from the heart are discussed, and the salient features of cardiac exposure are presented. Various techniques and approaches are outlined for removing foreign bodies from the chambers of the heart.

The author emphasizes that the mortality and morbidity rates for retained foreign bodies in and in relation to thoracic blood vessels and the heart have not been completely assessed. However, in this series of 134 patients who have had foreign bodies removed, there were no deaths and the men are clinically well.

NAIDE.

Junco, J. A.: 'The Cardiovascular Manifestations of Vitamin B Deficiency in the Children of Cuba: 1. The So-Called Borderline Case. Rev. cubana de cardiol. 6:143 (July-Dec.), 1945.

Vitamin B deficiency appears to be very common among the children of Cuba, especially among the poorer classes whose chief dietary component is maize. Several clinical forms have been described: (1) the borderline case; (2) the acute beriberi of the nursling; (3) pellagra-beriberi of childhood; (4) idiopathic cardiac hypertrophy.

The borderline case of vitamin B deficiency occurs in children of all ages and is characterized by bizarre symptoms referable to the gastrointestinal, nervous, cardiovascular, and cutaneous muscular systems. These may be vague and often defy strict classification. Hydrolability is a characteristic, appearing either as edema or dehydration.

Cardiac disturbances were found in 75 per cent of the cases studied. They consisted of dyspnea, tachycardia, muffled first sound, embryocardia, and, at times, gallop rhythm. Murmurs, arrhythmias, and cardiac enlargement were conspicuously absent. Serial electrocardiograms showed sinus tachycardia, low voltage, and low amplitude T waves in all leads, indicating myocardial damage. Both the clinical picture and the electrocardiogram returned to normal following adequate thiamine therapy, indicating that the cardiac changes were reversible and due to deficient intake of vitamin B₁.

GOLD.

Abrilli, A. J.: The Cardiovascular Manifestations of Vitamin B Deficiency in the Children of Cuba. 2. Acute Beriberi of the Nursling. Rev. cubana de cardiol. 6: 156 (July-Dec.), 1945.

Acute beriberi in the nursing infant in Cuba has been found to be more common than such childhood diseases as pyloric stenosis, intussusception, scurvy, and tetany. Abrilli reports on fifty-two infants, most of whom were between 3 and 4 months of age. The majority of them were breast fed but received inadequate feeding. The mothers had been receiving inadequate diets although none had clinical beriberi. The onset of the disease was abrupt and was usually precipitated by a minor upper respiratory infection. The symptoms were characterized by disturbances of the nervous and cardiovascular system and were toxic in origin.

The cardiovascular changes were present to some degree in all forms of the disease; in some these changes were the dominant feature. Labored breathing, cyanosis, pulse rates of 120 to 190 per minute, distant heart sounds, and tic-tac rhythm were observed. Occasionally true gallop rhythm was seen. In only one case was a systolic apical murmur heard. There were no arrhythmias, and no arterial bruits were observed as reported in adult beriberi. The peripheral veins were collapsed; the radial pulse was weak and of low volume. The liver was moderately enlarged, and basal râles were heard in 10 per cent of the cases.

T-wave changes in Leads I and II were always present. These waves were flat or diphasic; in one case they were inverted. In most cases the QRS complex was of low amplitude with alterations of the S-T segment.

Of the fifty-two cases, ten patients died, two because of intercurrent infection, the remainder as a result of inadequate treatment. The response to thiamine intravenously was spectacular. The symptoms and signs disappeared within a few hours; however, cardiac hypertrophy often took days or weeks to disappear. At necropsy, the heart was always found to be enlarged as a result of dilatation and hypertrophy. The myocardium was soft and flabby. The right auricular walls were not atrophied and the pulmonary conus was never distended. Histologically, interstitial edema with separation of muscle fibres and vacuolization of the latter was found. Round cell infiltration was observed in one case. The endocardium and pericardium were not involved.

It was concluded that there was no relation between the cardiac disturbance and the acidosis frequently present. The latter was associated with marked excretion of organic acids of the pyruvic acid type. There was no ketonuria which distinguishes this type of acidosis from the ordinary ketosis.

GOLD.

de los Reyes, R. P.: The Cardiovascular Manifestations of Vitamin B Deficiency in the Children of Cuba. 3. The Pellagra-Beriberi Syndrome. *Rev. cubana de cardiol.* 6:174 (July-Dec.), 1945.

The following clinical manifestations are present in the pellagra-beriberi syndrome: faulty development with loss in weight and height; cutaneous changes; mucosal pathology, especially of the tongue, mouth, palpebral, gastrointestinal, and vaginal tracts; gastrointestinal disorders (anorexia and diarrhea); disorders of the nervous system (changes in temperament, catalepsy, marked asthenia, abnormal reflexes); altered water metabolism (peripheral edema with a marked tendency to anhydremia); hepatic insufficiency; anemia, either hyperchromic, macrocytic, or hypochromic microcytic in type; change in the quality of the hair.

Cardiologic study revealed the same electrocardiographic findings reported by Junco and Abrilli (1 and 2), but cardiac enlargement was not found in the majority of the patients. In some cases, the heart was slightly enlarged, in others it was normal, and in several, the heart was small.

Reyes also studied the cardiologic changes in a control group of children suffering from anemia (parasitic, aplastic, posthemorrhagic and sickle-cell). The contrast with the pellagra beriberi heart of childhood was striking. In the former there was an almost consistent dilatation of the heart (either of the left or global) and frequent absence of electrocardiographic changes. Twenty-seven of the thirty-four patients studied had normal electrocardiographic tracings; of the other seven, five had tracings that resembled, somewhat, those seen in pellagra-beriberi, and in two there were marked alterations (one had A-V heart block). In addition, cardiac murmurs were the rule in this anemia group.

GOLD.

de la Torre, H.: The Cardiovascular Manifestations of Vitamin B Deficiency in the Children of Cuba. 4. The So-Called Idiopathic Cardiac Hypertrophy. *Rev. cubana de cardiol.* 6:191 (July-Dec.), 1945.

De la Torre reports six cases of idiopathic cardiac hypertrophy and calls attention to the possible etiologic role of vitamin B₁ deficiency. This is predicated upon the similarities in the clinical picture obtained in this disease and that of infantile beriberi. The cardiac findings are much alike in both disorders except that the enlargement of the heart (particularly of the left chamber) is much greater in the former. However, important differences exist between them. At autopsy, two of the cases of idiopathic hypertrophy showed endocardial fibrosis. In addition, one case also had marked proliferation of the interstitial connective tissue. A third autopsy also revealed marked cellular infiltration, proliferation of the connective tissue, and small vessel dilatation with focal compression of the muscle fibres. Such changes were never found in the

heart of acute beriberi. Finally, the therapeutic response of four patients to adequate doses of vitamin B₁ was considered satisfactory at one stage or another of the disease, but the size of the heart was not materially affected by the therapy and a great tendency toward relapse was noted. According to de la Torre, this is perhaps best explained on the basis of irreversible changes due to the degree and duration of vitamin B₁ deficiency encountered in these cases of idiopathic cardiac hypertrophy as compared to the acute beriberi of the nursing infant.

GOLD.

Owen, G. C., and Bradford, H. A.: The Prothrombinopenic Effect of Massive Salicylate Therapy in Acute Rheumatic Fever. Ann. Int. Med. 25: 97 (July), 1946.

Because of conflicting reports regarding the behavior of prothrombin activity in patients receiving large doses of salicylates, these authors undertook a study to determine the behavior of prothrombin in twenty-five patients with acute rheumatic fever treated by Coburn's method with large doses of salicylates. Their ages ranged from 18 to 40 years. All had been hospitalized for rheumatic fever in an acute state. The patients were given 10 Gm. of sodium salicylate in 1,000 c.c. of normal saline intravenously over a four-hour period daily for six days or longer, depending on the patient's clinical course. Those patients who failed to show a prompt response in symptoms, fever, and sedimentation rate were given an additional 10 Gm. of sodium salicylate daily. Thereafter, 10 Gm. of the drug were given orally each day in divided doses at four-hour intervals. Duration of treatment varied from twenty-one to sixty days. The Magath modification of the Quick method of determining the prothrombin time was used in these studies. By means of quantitative blood salicylate analyses made at three-day intervals, it was determined that concentrations of the drug were maintained at about 35 mg. in almost all cases.

Two effects of massive salicylate dosage on the blood prothrombin time were noted. A moderate prolongation of the prothrombin time occurred in all cases after the third or fourth day of treatment. Despite continuation of salicylates, there was a spontaneous and rather rapid return of the prothrombin time toward normal level. This tendency was noted as a general trend following the third week of therapy when the prothrombin time approached normal values despite the maintenance of high level of salicylate concentration in the blood. In five cases, bleeding, consisting of epistaxis or small nail bed hemorrhage, occurred at the time of maximum prolongation of the prothrombin time.

WENDKOS.

Lenegre, J., and Maurice, P.: First Recording of the Curves of Right Auricular and Ventricular Pressure in Man. Arch. d. mal. du coeur. 39: 24 (Jan.-Feb.), 1946.

The graphic registration of the pressure in the right auricle and ventricle in ten subjects is reported. The technique involved the introduction of a catheter into an antecubital vein and its passage into the auricle and ventricle. The end of the catheter was connected to a piezograph in such a manner that the pressure waves were transmitted to the surface of a variable condenser. This in turn was connected to a cathode ray oscillograph which recorded the curves.

It was found that in a subject who had no cardiac abnormality, the differential ventricular pressure was 23 mm. Hg, or 31 cm. water. The differential ventricular pressure varied considerably, however, in the presence of cardiac abnormality. It was normal or only slightly increased when the cardiopathy was well tolerated but extremely high when the cardiopathy was poorly tolerated. Occasionally it was very high, even when the mean pressure was scarcely changed. Marked variations in the differential pressure occurred when the catheter was near the tricuspid valve.

Differential pressure in the right auricle varied from 6 to 10 mm. of mercury.

The shape of the ventricular pressure curve during diastole was, in some cases, almost horizontal, while in others it was clearly ascending. During systole the plateau of the curve may be ascending, descending, or dome shaped. The auricular shock was sometimes very clear, but at other times indistinct.

It is pointed out that the number of cases studied is not yet sufficient to give very definite significance to the various forms of the curves which were recorded.

LAPLACE.

Wastl, H.: Influence of Two Thiourea Derivatives on Blood Pressure in Hypertensive Rats. Arch. internat. de pharmacodyn, et de therap. 71: 204, (Dec. 31), 1945.

This investigation involved a study of the influence of S-benzyl-iso-thiourea hydrochloride and S-methyl-iso-thiourea sulphate on the blood pressure in experimentally induced hypertension in rats.

The rats were rendered hypertensive by looping a cotton thread over the poles of both kidneys. The blood pressure was measured in the tail of the unanesthetized rat by the plethysmographic method. During the period of treatment with the drug which was administered intraperitoneally in aqueous solution, the blood pressure dropped in many of the hypertensive rats but not in the normal control rats. In the hypertensive rats, the extent of the blood pressure decline varied individually according to the degree of hypertension and according to the dose of the drug.

The optimum dose for both compounds was 0.5 mg. per kilogram. With this dose, the average blood pressure of all hypertensive animals declined from the first to the fourth day of treatment. The blood pressure returned to its preinjection level by the third day after cessation of the injections. The reduction of blood pressure was more pronounced with increasing degrees of hypertension. Of the two preparations, the S-benzyl derivative exhibited a more pronounced depressor action. Both compounds showed a certain degree of tachyphylaxis in the later days of the experiment. No trace of any adverse effect was observed.

It is suggested that in cases of essential hypertension in man, 1 mg. per kilogram of S-benzyl-iso-thiourea hydrochloride be administered orally.

LAPLACE.

Anrep, G. V., and Misrahy, G.: Ammi Visnaga as a Coronary Vasodilator. Gazette of the Faculty of Medicine, Cairo, Egypt (June), 1945.

The Khellin plant, which grows widely in Egypt, yields the drug *Ammi visnaga*. Of the principals extracted from *Ammi visnaga*, Visaminin proved to be the most important, and its action on isolated organs and on the whole animal was studied in detail.

Visaminin was found to have diuretic properties and proved capable of producing a relaxing effect on smooth muscle. In animals, intravenous administration caused a transitory fall in the blood pressure. In the heart-lung preparations, the authors found that Visaminin produced considerable increase in the coronary blood flow. They also found that 120 times the minimal amount necessary to produce coronary dilatation had no injurious effect on the heart muscle. No electrocardiographic changes were noted. The pulmonary blood pressure and the rate of the denervated heart were not affected.

The authors suggest the use of Visaminin in clinical practice as a coronary vasodilator and believe that it may prove to be superior to the caffeine and nitrite groups of drugs because of the prolonged action on the coronary arteries and because it does not lower the systemic blood pressure.

BELLET.

Kenawy, M. R., and Barsoum, G. S.: Ammi Visnaga in the Treatment of the Anginal Syndrome. Gazette of the Faculty of Medicine, Cairo, Egypt, 13:33 (June), 1945.

As a result of the experiments of Anrep and Misrahy, which showed that this drug is an exceptionally strong coronary vasodilator, it was decided to test its effect upon patients with the anginal syndrome. Six patients with angina pectoris were subjected to exercise tolerance tests. Electrocardiograms were taken before and following these tests, after which the drug was administered orally and intramuscularly. Considerable improvement was observed in the patients'

symptoms and signs, and in some instances the anginal seizures were abolished for long periods of time.

The authors believe that this drug has a selective effect on the coronary blood vessels and does not lower the blood pressure in man. In two cases, depression of the RS-T segment disappeared following the administration of Visaminin.

BELLET.

Neuhauser, E. B. D.: The Roentgen Diagnosis of Double Aortic Arch and Other Anomalies of the Great Vessels. Am. J. Roentgenol. 56:1 (July), 1946.

Symptoms of dysphagia, wheezing, stridor, or recurrent tracheobronchitis or pneumonia are indications for careful roentgenologic examination for anomalies of the great vessels. These congenital defects are not rare and are now, in many instances, amenable to cure or improvement by surgical intervention.

In addition to situs inversus, two types of right aortic arch without inversion are described. In the anterior type the aortic arch is anterior to the trachea and the descending aorta is on the right side. In the posterior type the aorta passes to the left behind the esophagus and the descending aorta is on the right of the normal left-sided position. On roentgen examination, the anterior right arch without inversion is found to produce a defect on the right side of the esophagus. There is no defect on the posterior aspect of the esophagus. This type of arch deformity alone does not produce symptoms.

The posterior right aortic arch may be of three types. In the first type, the left subclavian artery arises last from the arch and crosses behind the esophagus. In the second type, no vessel arises from the arch to cross the midline posterior to the esophagus. In the third type, there is a persistent left aortic diverticulum giving origin to the left subclavian artery. The basic deformity in the posterior right aortic arch consists of deviation of the esophagus to the left, a rounded defect on the right lateral aspect of the esophagus, and a rounded defect on the posterior aspect of the esophagus.

Double aortic arch of the constricting type produces a rather characteristic clinical picture in infants, although the diagnosis rests solely on roentgenographic examination. The onset of symptoms usually occurs in infancy and the patients with this syndrome usually present stridorous breathing, mild dysphagia, head retraction, chronic cough, and frequent attacks of pulmonary infection. The stridor is usually made worse by feeding. Four cases of this type from the Children's Hospital in Boston are reported. In these cases, no abnormality could be detected in the posteroanterior projection without the aid of contrast substance, since it is extremely difficult to visualize the position of the aortic arch in infants. In the lateral projection, it is impossible to see narrowing and anterior displacement of the trachea at the level of the aortic arch while the posterior right arch produced forward displacement of the barium-filled esophagus. The anteroposterior projection reveals narrowing of the esophagus from both the right and left sides due to pressure of the vascular ring, but there is no deviation of the esophagus to the left as seen with right aortic arch alone. A deformity of the trachea is likewise seen after the introduction of an opaque oil. The trachea is displaced forward at the level of the right aortic arch and is narrowed from both the right and left sides by pressure of the vascular ring, and pressed upon anteriorly by the left aortic ring.

BELLET.

Matthewson, F. A. L., and Sellers, A. H.: Electrocardiograms of Older Pilots. J. Aviation Med. 17:207 (June), 1946.

Electrocardiographic data were collected on a series of 328 fliers who were 35 years of age and over. Analysis of the records revealed that ten of this group showed premature beats which were auricular in two instances and ventricular in eight. Ten showed a prolongation of the P-R interval slightly in excess of 0.20 second; six showed a P-R interval of 0.22 second or greater; and at least two exhibited the Wenkebach phenomenon. In seven fliers, the QRS interval was in excess of 0.10 second. Twelve showed deep Q waves, which were present in Lead I in three instances and in Lead III in nine. There were no instances of inversion of T waves in Leads I or II.

In the entire group, probable heart disease was detected by electrocardiography in two subjects. One of these showed left bundle branch block and the other showed abnormal T waves in Leads I and IV.

BELLETT.

Lester, D., Lolli, G., and Greenberg, L. A.: The Fate of Acetylsalicylic Acid. *J. Pharmacol. & Exper. Therap.* 87:329 (August), 1946.

This investigation deals with the behavior of the smaller doses of acetylsalicylic acid used as analgesics. It includes a study of the excretion, the forms, and concentrations in which salicylate appears in the plasma; the influence of bicarbonate upon absorption, plasma concentration, elimination, and accumulation of salicylate; the binding of salicylate by plasma; the distribution of salicylates in the body fluids; and the nature of the excretion of salicylates by the kidneys. Salicylate analgesia is also discussed.

The subjects were men who were mainly healthy laboratory personnel. The duration and amount of excretion of salicylate in the urine were determined after oral administration of 0.33 to 1.95 Gm. of acetylsalicylic acid. From 52 to 75 per cent of the acetylsalicylic acid ingested was found to be excreted in the urine in various forms. The time required for excretion ranged from fifteen hours for doses of 0.33 Gm. to thirty hours for doses of 1.95 Gm. The maximum concentration of total salicylate in the plasma was of the order of 4 mg. per cent after doses of 0.65 Gm. The plasma concentration bore an approximately linear relationship to the dosage.

The coincident administration of bicarbonate increased the rate of absorption of acetylsalicylic acid. This action does not alter the level of the maximum concentration that is reached in the plasma but does enable the maximum concentration to develop earlier. Bicarbonate also increased the rate of elimination of salicylate and hence the rate of decrease in concentration after the attainment of the maximum level.

In patients with rheumatic fever who are receiving salicylate therapy, a much lower per cent of salicylate is bound by the plasma than in normal individuals. In one instance only 6 per cent was bound at a total plasma concentration of salicylic acid of 37 mg. per cent. The binding of salicylate with protein decreases with decrease in concentration of protein, but the ratio increases and varies linearly with the concentration of protein.

Temperature exerts no effect upon the extent of the binding of the salicylate by protein. It was found that the binding power of plasma for free salicylate is much higher than for acetylsalicylate. The distribution between the plasma and the red cells and the peritoneal saline and cerebrospinal fluid was determined by the unbound fraction of plasma water. Acetylsalicylic acid is rapidly hydrolyzed after absorption, but up to a period of one to two hours as much as one-quarter of the salicylate in the plasma may be in the acetylated form.

The theory is advanced that the analgesic action of the acetylsalicylate is exercised mainly by the unhydrolyzed acetylated fraction in the plasma. If this hypothesis regarding the analgesic action is valid, the simultaneous administration of bicarbonate would have a beneficial effect in hastening the absorption and therefore speeding the analgesia. Since the duration is relatively short, a more rapid excretion of the salicylate caused by the bicarbonate may be advantageous.

BELLETT.

Battro, A., and Mendy, J. C.: Precordial Leads in Children. *Arch. Int. Med.* 78:31 (July), 1946.

These authors performed electrocardiographic studies on fifty healthy children whom they divided into three age groups: A (up to 2 years), B (3 to 5 years), and C (6 to 10 years). Besides the standard leads, six precordial leads (V_1 , V_2 , V_3 , V_4 , V_5 , and V_6), as well as the unipolar limb leads (V_R , V_L , and V_F), were recorded by using the Wilson terminal electrode. In Group A, the R wave was often greater than the S wave in Lead V_1 . This predominance of the R wave frequently persisted through Lead V_5 , and thus differed appreciably from the findings in the precordial electrocardiogram of the normal adult. In Group B, the R and S waves tended to be

of equal amplitude in leads to the left and the right of the sternum. This finding in children of this age represents a form of transition between the configuration seen in Group A and that found in Group C. In Group C, the relative size of the R and S waves was fairly similar to the "adult type," with definite predominance of the S over the R wave in Lead V_1 and of the R over the S wave in Lead V_6 .

The alterations of the T wave were as follows: in Group A, the T waves were frequently negative or diphasic even through Lead V_6 . In Group B, negative or diphasic T waves were observed through Lead V_6 , although this configuration was less frequently observed than in Group A. In Group C, negative T waves were not observed in Leads V_5 and V_6 . The degree of negativity of the T wave usually decreased gradually in the three groups from Leads V_1 to V_6 , with the exception of V_2 , in which the negativity sometimes was greater than in Lead V_1 .

BELLET.

Ravin, A., and Geever, E. F.: Coronary Arteriosclerosis, Coronary Anastomoses and Myocardial Infarction. Arch. Int. Med. 78:125 (August), 1946.

The authors examined 166 hearts by the Schlesinger method. This technique involves cannulation of the right and left coronary arteries of the unembalmed heart and injection of a mixture of agar and a lead salt into these arteries. The mass injected into the respective arteries was given a different color. The injected mass passes through arterioles 40 microns in diameter and reaches about 50 per cent of the vessels 20 microns in diameter. Except for instances in which the diagnosis was obvious, the series was unselected and included a wide range of pathologic conditions as well as many normal hearts.

The ages of the patients varied from 1 to 90 years, the majority being in the range of 40 to 70 years. The failure of the colors to mix indicated that in the normal hearts, at least, there were no anastomotic vessels greater than 20 to 40 microns in diameter. When anastomotic vessels greater than 20 microns in diameter were present, the masses and their colors were mixed.

Interarterial anastomoses were found in thirty-six hearts. Occlusion of the coronary arteries was found in eighteen hearts. Seven specimens revealed more than one occluded vessel. Occlusion without infarction was present in five hearts and occlusion with infarction, in thirteen hearts. Infarction without occlusion of a coronary artery was observed in two hearts.

BELLET.

Errata

In the September, 1946, issue of the AMERICAN HEART JOURNAL two errors appeared which we wish to correct:

In the abstract of the paper entitled "Electrokymograph for Recording Heart Motion Utilizing the Roentgenoscope," Am. J. Roentgenol. 54: 217 (Sept.), 1945, the names of the two authors should read Henny, G. C., and Boone, B. R., instead of Henry, G. C., and Boone, A. A.

The phrase at the end of the fourth line of the second paragraph should read "*without distortion*" instead of "with distortion."

Book Reviews

RENAL HYPERTENSION. By Eduardo Braun-Menéndez, Juan Carlos Fasciolo, Luis F. Leboir, Juan Muñoz, and Alberto C. Taquini. Translated by Lewis Dexter. Springfield, Ill., 1946, Charles C. Thomas, Publishers.

By making this book available in English, Dr. Dexter has performed a great service to clinicians and experimenters interested in the subject of hypertension. By permitting Dr. Dexter to incorporate his own ideas and to include the additional work that has been performed on this subject since the appearance of the first edition, in 1943, in Spanish, the authors have enabled him to bring the whole subject up to date. Although the original authors and the translator have written the book from the particular point of view to which they adhere, yet in their critical evaluation of all the work on the subject, they have been eminently fair. The concept of the renal, and probably humoral, origin of most cases of so-called essential hypertension dominates the book, but an excellent historical survey is included and a good discussion of all other views is given. No brief summary of this book, which would be of any value, is possible. An important part of the book for other investigators is the appendix, which gives the details of the various methods developed and used by the authors in their own studies of experimental renal and human hypertension, especially the preparation and assay of the various constituents of the humoral mechanism. Since Dr. Dexter states that he did not attempt "To produce a line for line translation of the book," no comment on the exactness of this translation is necessary. Although the reviewer is unfamiliar with Spanish, yet his knowledge of the important contributions of the authors to the subject of hypertension makes it possible for him to state unequivocally that Dr. Dexter has certainly presented a correct version of their views. The book is well written and the illustrations, although many are reproductions of illustrations in other books and journals, are well chosen and entirely adequate. This book should be regarded as an outstanding contribution to the subject of hypertension in general and experimental renal hypertension in particular.

HARRY GOLDBLATT.

On Oct. 16, 1946, occurred the first public demonstration of the relief of the pain of surgery by ether vapors. The Centenary of this great contribution to the world is being commemorated by three publications which will be reviewed here.

VICTORY OVER PAIN. By Victor Robinson, M.D. New York, 1946, Schuman's ed 1.

This is a history of anesthesia ostensibly, but it is far more than that. Dr. Robinson has a stirring tale to tell and does full justice to it. Drama, controversy, despair, and bitterness, as well as triumph, characterize the volume. The great characters in medicine of the nineteenth century relive. American, English, Scottish, French, German, and Russian medical circles are portrayed with fascinating detail. The presentation abounds with anecdotes and with letters interpreted with insight and perspective. The whole story is humanized by a master of medical history. *Victory Over Pain* should be required reading for physicians, and also for thinking people in all circles. It recounts the hazards and disappointments of research. It emphasizes the price of the failure to recognize the significance of new observations. It describes the struggles for fame and fortune occasioned by the difficulty of establishing priority for a discovery. More than this, the book can be regarded as contributing to our understanding of the relationship of the sciences to humanity.

As stated by the publishers, "We are all aware that scientific advances have reached a point where they dominate the lives and destiny of everyone. With this awareness has come a natural desire to understand more fully the role and impact of science on our everyday life." Anesthesia must be considered among the major contributions of man to his fellow men. It is fitting and proper that its story be recounted for all to appreciate.

Readable, lucid, instructive and entertaining, this volume is unhesitatingly recommended to physicians whatever their special interest.

ROBERT D. DRIPPS, M.D.

A MEMOIR ON A NEW USE OF SULFURIC ETHER. By W. T. G. Morton. New York, 1946, Schuman's.

For one hundred years the controversy over who discovered and introduced surgical anesthesia has continued. Long, Wells, Jackson, and Morton have been the chief figures in this unfortunate dispute. This little monograph presents Morton's attempt to justify his claims. It is the first separate reprinting of his celebrated letter to the Academy of Sciences at Paris. The reprinting is amply justified as a contribution to the ether centennial. It strongly supports the contention of those who establish William T. Green Morton as the individual who first realized the *significance* of the ability of ether to relieve the pain of surgical intervention.

ROBERT D. DRIPPS, M.D.

THE CENTENNIAL OF SURGICAL ANESTHESIA, AN ANNOTATED CATALOGUE. Compiled by John F. Fulton, M.D., and Madeline E. Stanton, A.B. New York, 1946, Schuman's.

The final contribution by this particular publisher to the ether centennial is the annotated catalogue of the early writings on anesthesia prepared for an exhibit at the Yale School of Medicine. There is an introduction and pertinent comment by John F. Fulton, Professor of Physiology at Yale. This catalogue would be of interest primarily to historians or others concerned with the details of the story of anesthesia.

ROBERT D. DRIPPS, M.D.

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A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

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The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

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The Association earnestly solicits your support and suggestions for its work. Membership-application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

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INCIDENCE OF ACUTE CORONARY ARTERY OCCLUSION

A DISCUSSION OF THE FACTORS RESPONSIBLE FOR ITS INCREASE

ARTHUR M. MASTER, M.D.
NEW YORK, N. Y.

IT HAS become inescapably clear that heart disease has been, since 1912, the chief cause of death in this country.¹⁻⁴ In 1942 almost 400,000 persons died of cardiac disease alone, about 28.5 per cent of all deaths.² It is probable that at least 4,000,000 persons are afflicted with heart disease. One survey gives an estimate of double this figure, placing the total at 8,000,000.⁵

PREVALENCE OF CORONARY ARTERY DISEASE

In any analysis of cardiac disease, the increase in coronary artery disease that has taken place during the last thirty years is especially striking. It has become the most important of the heart diseases. In 1942, deaths throughout the country from diseases of the coronary arteries and angina pectoris attained the highest figure on record, 113,636.² Coronary artery disease is thus the cause of 8.5 per cent of all deaths, the most common cause of mortality in this country with the exception of cancer. According to Clawson,⁶ 30 per cent of patients with organic heart disease have coronary artery involvement. Levy, Bruenn, and Kurtz⁷ give a percentage of 25.9. White⁸ estimates a figure of 37 per cent. *Vital Statistics of the United States, 1942*, report 30 per cent.² From these figures, it would appear that coronary artery disease comprises about one-third of all heart ailments. That this proportion is probably a conservative one is emphasized by a necropsy study in 1937 and 1938 of patients who died of heart disease in a large hospital in New York.⁹ Fifty-four per cent of the deaths were

attributable to disease of the coronary arteries. In this institution, every effort was made to determine accurate diagnoses during post-mortem examination of the heart; it seems reasonable to predict that this percentage will be corroborated in future examinations.

PREVALENCE OF ACUTE CORONARY ARTERY OCCLUSION

Figures on the prevalence of acute coronary artery occlusion cannot be obtained from the United States Census reports or, in fact, from any other source. The Census has no specific listing for acute coronary occlusion or thrombosis; it lists only diseases of the coronary arteries and angina pectoris. Unfortunately, even mortality due to the latter is not properly recorded, because in the *Manual of the International List of Causes of Death and Joint Causes of Death*,¹⁰ one disease is given greater weight than another. "Myocarditis" takes precedence over coronary artery disease and hence, as Hedley¹¹ points out, if the death certificate carries the diagnosis of "myocarditis and acute coronary thrombosis," the death is recorded as myocarditis, even though the attending physician may have considered it due to acute coronary thrombosis. Similarly, "nephritis" is given precedence over coronary disease. Hedley's investigation revealed that in 259 death certificates in which acute coronary thrombosis was diagnosed as the cause of death (in 144 as primary and in 115 as secondary), the official tabulation ascribed death to involvement of the coronary artery in only seventy-eight instances.

Since official records do not afford accurate statistics on the subject, information must be sought from other sources if we are to have a true picture of the incidence of acute coronary artery occlusion or thrombosis. In 1939, my colleagues and I¹² worked out a basis for computing the occurrence of these diseases. The figures that we presented at that time will be now brought up-to-date and some significant additions will be made.

In sampling death certificates of the state of New York,* it was observed that at least 25 per cent of the deaths reported in the *Manual of the International List of Causes of Death and Joint Causes of Death* under "Diseases of the Myocardium (Not Rheumatic)" were instances of acute coronary artery occlusion and that at least 60 per cent of the deaths ascribed to "coronary disease" and 80 per cent of those attributed to "angina pectoris" were instances of acute coronary occlusion. Assuming that these percentages hold good for the whole country, the number of cases of acute coronary occlusion in the United States for 1942 may be calculated. During 1942, there were 200,851 deaths from diseases of the myocardium (excluding rheumatic), 107,273 from diseases of the coronary arteries, and 6,363 from angina pectoris.¹³ Multiplying these figures by 25, 60, and 80 per cent, respectively, the total number of deaths from acute coronary occlusion was 119,666, or practically 120,000.

The figure of 120,000 deaths in 1942, the result of acute coronary artery occlusion, is truly conservative. Deaths listed under the headings "Other

*With the collaboration of J. V. DePorte, Director, Division of Vital Statistics, New York State Department of Health.

Diseases of the Heart (Not Rheumatic)" and "Functional Diseases of the Heart" (Numbers 95c and 95a, respectively, in the *Manual of the International List of Causes of Death and Joint Causes of Death*) were not included in our sampling, and many of these were probably cases of acute coronary occlusion.

Assuming that the mortality rate for acute coronary artery occlusion is 20 per cent, 120,000 deaths indicate that 600,000 attacks occurred in 1942. If a mortality rate of 15 per cent is chosen, then the incidence of attacks is 800,000, a figure that is, I believe, nearer the truth.

Since acute coronary occlusion is chiefly a disease of persons over 40 years of age, its incidence in individuals over this age is of interest. Approximately 34 per cent of the people in this country are in the age group over 40 years; that is, 23,000,000 men and about the same number of women. However, coronary disease is more common in men than in women. In recent clinical investigations,¹⁴ the ratio was about 3.5 to 1, whereas the Census tallies² indicate that the number of male deaths from coronary artery disease is not quite 2.5 times as many as the number of female deaths. Taking an average of 3 to 1, we find that of 800,000 attacks, 600,000 will occur in men and 200,000 in women. This means that every year, roughly 1 man in 38, 40 years of age and over, and 1 woman in 115, in the same age group, sustain closure of a coronary artery. If the incidence of acute coronary artery occlusion is accepted as 600,000, then the incidence becomes roughly 1 man in 50 and 1 woman in 150.

To the objection that, because of World War II, 1942 is not as representative a year as 1941, let me say that the United States Census figures for both years are practically the same.¹³ In 1942, the number in the Armed Force overseas was not large. Furthermore, the United States Census often takes into consideration troops overseas.¹³

Mortality Rate in Acute Coronary Occlusion.—Recent reports¹⁵⁻¹⁸ indicate that duration of life following acute coronary occlusion is much longer than it was earlier believed to be. Early reports described mortality rates of from 35 to 65 per cent in acute coronary occlusion.^{15,19,20,21} Since 1930, the figures have been much lower. Conner and Holt,¹⁵ in 1930, indicated that the rate might be as low as 16 per cent in first attacks. My colleagues and I,¹⁶ in a series of 267 cases, found that the rate for all cases was 16.5 per cent, and only 8 per cent in first attacks. Levine²² recently quoted rates of 15 to 25 per cent. It must be remembered that the most seriously ill patients, among whom the death rate will be high, are observed in the wards of hospitals, and most of the published reports are based on hospital records. Patients not so ill are more often seen at home. I believe that if all cases of acute coronary artery occlusion were reported, the mortality rate would prove to be less than 20 per cent, and, for the first attack, less than 10 per cent.

INCREASE IN CORONARY DISEASES

Increase in the prevalence of coronary artery disease, and more particularly acute coronary occlusion, is attributable to (1) lengthened span of life, (2) ageing

of the population, (3) improved diagnosis and treatment, and (4) accuracy in terminology.

Lengthened Span of Life.—The principal factor underlying the increase in coronary disease is the lengthening span of life which has taken place, notably in the past fifty years.

According to Dublin and Lotka,²³ the citizens of Rome in its halcyon days enjoyed a life span of but twenty to thirty years. In the beginning of the nineteenth century, "an average length of life of thirty-five to forty years may have been common in various localities among civilized nations."

Among Metropolitan Life Insurance industrial policyholders,²⁴ the life span between 1912 and 1944 has increased almost eighteen years and, since the decade 1879 to 1889, thirty years (Table I).

TABLE I. INCREASE IN LIFE SPAN BETWEEN THE YEARS 1879 AND 1944

YEAR	LIFE SPAN (YR.)
1879-1889	34.00
1911-1912	46.63
1919-1920	51.14
1930	57.36
1940	62.93
1944	64.40

How has the span of life been so augmented that it has almost attained the Biblical three score and ten? First, there has been a significant reduction in infectious disease.² The pneumonia and influenza death rate in 1900, per 100,000 population, was 202; in 1942, it had dropped to 55.7. In the same interval, the tuberculosis rate had fallen from 174.5 to 39.6; diarrhea and enteritis, from 142.7 to 8.8; diphtheria, from 40.3 to 1.0; typhoid and paratyphoid, from 31.5 to 0.6; whooping cough, from 12.2 to 1.9; scarlet fever, from 9.6 to 0.3.

New drugs are affording invaluable aid in controlling diseases that heretofore carried a high mortality. The figures in Table II, cited by Morgan,²⁵ show the role played by the sulfonamide drugs and penicillin in World War II.

TABLE II. COMPARISON OF FATALITIES IN WORLD WAR I AND WORLD WAR II

DISEASE	FATALITY IN PER CENT	
	WORLD WAR I	WORLD WAR II
Meningitis	38.0	4.0
Pneumonia	28.0	0.7
Tuberculosis	17.3	1.8
Dysentery	1.6	0.05

This dramatic reduction in infectious disease will continue with the increasing use of the sulfonamides and penicillin, and particularly of streptomycin. Streptomycin, it appears, will help to counteract the diseases now considered resistant to the sulfonamide drugs and to penicillin; for example, typhoid and tuberculosis.

Advance in medical knowledge with its improvements in surgical and medical treatment of disease as well as in diagnosis has saved the lives of millions of people, thus increasing the life span. The prophylactic measures taken by the Army to prevent and control such diseases as malaria, tetanus, typhoid, typhus, and cholera practically eliminated these formerly devastating diseases.

Progress in public health and sanitation, particularly in the fields of water and milk supply, disposal of sewage and waste, and nutrition, has contributed largely to reduction of infectious diseases. Nutritional diseases, such as pellagra, rickets, scurvy, and beriberi, have been brought under control. Improved ventilation and heating in factories and workshops have also made their contribution to longer life.

Ageing of the Population.—Growth in size of the older age groups in the population is another cause for the greater frequency with which coronary artery disease has been observed in recent years. In the United States in 1850, 8.9 per cent of the people were 50 years of age and older; in 1930, the rate had risen to 17.2 per cent.²⁶ According to the National Resources Planning Board,²⁶ there were, in 1900, 8,500,000 persons between the ages of 50 and 74; in 1940, 24,000,000; and in 1980, there will be 42,000,000. As we have seen, it is in this older age group that two-thirds of the episodes of acute coronary occlusion occur. Another factor in the ageing of the population has been the decline in birth rate of this country.

Improved Diagnosis and Treatment.—Previous to the publication of Herrick's reports in 1912, 1918, and 1919,²⁷⁻²⁹ acute coronary occlusion had not been recognized as a specific cardiac condition. Today, thanks to Herrick, Levine, and Tranter,³⁰ Libman,^{31,32} Pardee,³³ Smith,³⁴ Wolferth and Wood,³⁵ Wilson and colleagues,³⁶ Parkinson and Bedford,³⁷ and others, the clinical diagnosis of acute coronary occlusion is as well-defined as that of acute appendicitis.

The electrocardiogram is a potent aid in the diagnosis of acute coronary artery occlusion. It will often demonstrate acute coronary occlusion when the condition is not suspected or when the diagnosis is in doubt. "Acute indigestion," gall bladder disease, pneumonia, and stomach ulcer are much less frequently mistaken for acute coronary occlusion than they used to be.

The x-ray machine, the kymograph,³⁸ and the fluoroscope³⁹ are additional aids in the diagnosis of coronary disease.

Advances in medical knowledge have resulted not only in early recognition of acute coronary artery occlusion, but also in more effective methods of treating patients with this condition. With insistence on immediate bed rest,²⁷ avoidance of overtreatment with drugs, and a low calorie intake,^{16,40,41} early in the attack, the mortality rate has fallen. These preventive measures have not given the dramatic results that have followed the introduction of new drugs in infectious diseases, but they have saved untold numbers of lives; I take pride in

having been a pioneer in this newer treatment of acute coronary artery occlusion. Not long ago, patients suffering an attack of acute coronary occlusion received powerful drugs almost routinely: digitalis and often adrenalin, strychnine, and camphor. Although extremely ill, the patient was given a "cardiac diet," which consisted of 3,000 to 4,000 calories, with emphasis on carbohydrates because the specialized conduction tissue of the heart was believed to contain much glycogen.

Accuracy in Terminology.—The terms "coronary" disease and "angina pectoris due to coronary disease"⁴² have replaced such obsolete and vague expressions as "myocarditis," "cardiac dilatation," "heart failure," "chronic cardiac," "dropsy," and "senility." Since these ambiguous diagnoses have disappeared and definitive diagnoses have come into use, records show an automatic increase in the frequency of coronary disease.⁴¹

DISCUSSION

If we turn to the older statistics and compare them with recent ones, there has been an apparent startling increase in coronary disease. From the year 1930, the gain in disease of the coronary arteries appears phenomenal. Thus, according to United States Census enumerations,⁴³ there were 28,286 deaths in 1930 from diseases of the coronary arteries and angina pectoris, but in 1940 the figure was 101,463. In the ten-year period 1930 to 1940, the Metropolitan Life Insurance Company reported a doubling in the number of persons suffering from this disease.⁴⁴ Dublin and Lotka²³ recorded a "perpendicular rise" from 5.6 per 100,000 in 1930 to 23.1 in 1935, an increment of more than 300 per cent. Denny⁴⁵ and also Willius⁴⁶ reported a similar amazing growth of coronary disease. It is obvious that the growth in this decade is out of line and cannot be a true increase. It is, of course, explained in part by the fact that previous to 1930, acute coronary occlusion was not too readily recognized, and it was not until 1930 that the disease began to be listed.^{1,4,7,47,48,49,50} Ageing of the population is another contributing factor.^{51,52} However, the increase in coronary disease, or, specifically, acute coronary occlusion, has been due in large measure to increase in life span, improvement in diagnosis, and more adequate treatment of the patients.

There are many physicians who are still of the opinion that there has been a true increase in coronary disease and cite stress and strain of modern life, anxiety states, abuse of tobacco, and overweight as causative factors.⁵³ I do not subscribe to this theory. Stress and strain today is not greater than that which existed in ancient times, during periods of wars, great fires, plagues, and famines. In fact, people work shorter hours and in greater comfort. Moreover, our investigations⁵⁴⁻⁵⁶ have revealed that acute coronary occlusion is not a respecter of persons: rich and poor, the laborer, the executive, or the ordinary man at the desk are all possible victims.⁵⁴⁻⁵⁶

For many years it has been said that doctors are particularly prone to acute coronary thrombosis.⁵⁷ Musser⁵⁸ believed that coronary arterial disease was properly called "the doctor's disease." A study of obituaries of physicians as reviewed yearly in the *Journal of the American Medical Association*⁵⁹ might lead the unwary to gain this impression, since the numbers dying from this disease appears

at first sight to be large. Those who believe that doctors are especially liable to die of acute coronary thrombosis give as the cause the sedentary nature of their occupation. Yet there are not harder working persons than members of the medical profession. My associates and I have already made a comparison of the occupations of our patients suffering from acute coronary occlusion with the occupations of the population as listed in the United States Census, and the results of our investigation yielded no significant difference in the relative proportions.⁵⁴⁻⁵⁵ The professional class, including physicians, was represented no more and no less than one would expect from their numbers in the general population. Recently, other authors have examined the question of coronary disease among physicians and reached the same conclusions that we did. Falk⁶⁰ believes that the apparent increase in coronary artery disease among doctors is accounted for by "a more accurate diagnostic trend." Fitz⁶¹ estimated the age distribution of American physicians from 1907 to 1942 and found that they, like others, were living longer and that the prevalence of coronary disease among them had risen correspondingly. Levine and Hindle⁶² reported that the average age at death of physicians dying from coronary disease did not differ from the average age of lay persons who were victims of this disease. The fact is that physicians who live long enough may sustain acute coronary occlusion but in no greater or lesser numbers than other persons of the same age.⁵⁵

Tobacco is, of course, perennially held responsible for heart disease.^{53,63} White and Sharber⁶⁴ investigated the relationship of tobacco and alcohol to angina pectoris and concluded that neither played an important role in the genesis of this cardiac disease. Blumer⁶⁵ arrived at a similar conclusion in respect to acute coronary occlusion. My associates and I,⁵⁴ in an analysis of the histories of 364 patients with acute coronary artery thrombosis, found that one-third of the men and practically all of the women were nonsmokers. As the proportion of heavy and moderate smokers in this group of patients did not differ from the ratio in the general population, it may be assumed that the use of tobacco was not influential in precipitating the attacks of acute coronary thrombosis.

At present, figures showing the incidence of acute coronary thrombosis can at best be only an estimate, but we are approaching closer to the actual facts. But if statistics are to reflect accurately the status of acute coronary occlusion, it must be kept in mind that there is more than one type of arteriosclerotic coronary artery disease; that is, there are *coronary artery diseases* rather than a coronary artery disease.⁶⁶ There are, for example, the simple episode of angina pectoris, the acute attack of coronary occlusion, and, finally, myocardial necrosis without occlusion.⁶⁷ The importance of distinguishing these types of coronary artery disease cannot be emphasized too strongly, for the next step should be to distinguish sharply between myocardial infarction due to acute coronary occlusion and the myocardial necrosis without occlusion. Their precipitating causes, pathology, electrocardiograms, and treatment differ.⁶⁶

The present high incidence of coronary disease should not be cause for pessimism but rather an impetus to further research. Progress in medicine, public health, and sanitation has brought about a decline in the number of deaths

in infancy, childhood, and even in adult life and in old age. The life span has been lengthened with a concomitant increase in diseases of old age. Yet there is still much knowledge needed if the ill health due to heart disease is to be alleviated. As Dublin⁶⁸ said, "No other disease (coronary artery disease) in the entire field of medicine, with the possible exception of cancer, offers so large an opportunity for life-saving service."

Dublin and Lotka,²³ in 1936, hypothesized an eventual expectation of life at birth of 70 years. Of course, after birth this would go beyond 70 years. Piersol⁶⁹ surmised that by 1960 a boy might expect to live to 75 years and a girl to 80 years of age or more. With advances in medicine, particularly since the advent of the sulfonamide drugs, penicillin and streptomycin, it is not improbable that arteriosclerotic disease may be delayed and the life span become five score.

SUMMARY

Heart disease is the chief cause of death in the United States. Nearly 400,000 persons die yearly of cardiac disease. This comprises almost 30 per cent of all deaths.

Coronary artery disease alone is the greatest cause of mortality except cancer. Eight and one-half per cent of all deaths result from this condition. Approximately 114,000 persons die annually of coronary disease.

Of cardiac fatalities, those due to coronary disease are estimated to be from 30 to 50 per cent.

Acute coronary occlusion or thrombosis is not listed separately in the Census but is included under "Diseases of the Coronary Arteries" and "Angina Pectoris." The estimation of the actual number of deaths from acute coronary occlusion presented in this paper was made by sampling New York State death certificates and by applying the figures thus derived to the rest of the country. It was computed that at least 25 per cent of deaths reported under "Diseases of the Myocardium," 60 per cent of those ascribed to "Coronary Disease," and 80 per cent of those listed as "Angina Pectoris" were, in fact, instances of acute coronary occlusion. On the basis of these percentages, it is estimated that there were 120,000 deaths from acute coronary occlusion in this country in 1942. If the mortality rate for this disease is accepted as 15 per cent, there are about 800,000 attacks of acute coronary occlusion yearly.

Using the United States Census figures for the number of men and women in this country over 40 years of age, and an incidence ratio of 3 men to 1 woman, we may conclude that approximately 1 man in 40 and 1 woman in 115 experience an attack of acute coronary occlusion yearly. These figures will, of course, vary if other mortality rates are adopted for the computation. There is some evidence that the number of instances of acute coronary occlusion may be as high as 1,000,000; if this figure is accepted, 1 man in 30 and 1 woman in 90, 40 years of age and over, annually sustain acute complete obstruction of a coronary artery.

The increase in diseases of the coronary arteries is explained by the increased span of life brought about by reduction in infectious disease of childhood and adult life, advances in medical knowledge, and improvement in public health

and sanitation. The numbers of persons suffering from coronary disease will continue to increase with the relative increase in older age groups, decline in birth rate, improvement in diagnosis, more effective treatment of coronary disease, and, indirectly, by the use of correct terminology.

The startling increase in incidence of acute coronary occlusion since 1930 is due to better reporting of coronary disease since that year.

There is no evidence that stress and strain of modern life or the use of tobacco or alcohol are factors in the production of disease of the coronary arteries.

Physicians are not more prone to acute coronary occlusion than are other persons. It should no longer be thought of as the "doctor's disease."

With the use of the sulfonamide drugs, penicillin, and streptomycin, the span of life will increase, and, therefore, the incidence of acute coronary disease will continue to rise. This magnitude of the incidence of coronary disease is a challenge to further research.

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COARCTATION OF THE AORTA

A REVIEW OF 104 AUTOPSIED CASES OF THE "ADULT TYPE," 2 YEARS OF AGE OR OLDER

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POSSIBLE surgical treatment of coarctation of the aorta^{120,122,127,135} stimulated this analysis of autopsied cases that have been collected since Abbott's review in 1928.¹¹⁹ Causes of death, cardiovascular findings, and conclusions regarding life expectancy are presented.

Coarctation is not a common lesion. The probable incidence of the adult type is 1 per 3,000 or 4,000 or more autopsies. The diagnosis is being made more frequently during the life of the patient because of numerous clinical, radiologic, and physiologic studies.

Most cases may be classified into one of two groups: (1) cases in which the coarctation commonly is accompanied by major congenital cardiac anomalies, the infant not surviving more than days or weeks, and (2) cases in which coarctation is the major or sole anomaly, the patient living over a period of years. In the former group, sometimes called the "infantile" type, the constricted aortic segment usually diffusely involves the entire region of the fetal isthmus (from the origin of the left subclavian artery to the site of insertion of the ductus arteriosus) and the associated serious cardiac anomalies usually preclude normal cardiac function. The latter group, sometimes called the "adult" type, occurs as a more focal area of constriction, usually 1 cm. or less in length, in the same region, most frequently at or just below (rarely above) the insertion of the ligamentum arteriosum. In these cases the effect on the heart and circulation is the result of aortic obstruction. The adult type has been described in infants¹⁵⁹ and the infantile type, in adults. Combined forms occur.

Because this survey was made from the viewpoint of possible surgical treatment, the cases included were of the adult type with moderate, extreme, or complete (atresic) constriction of the aorta. Cases of slight coarctation were omitted as these had circulatory changes which probably were insufficient to make possible an ante-mortem diagnosis. One exception⁴⁶ in which such a diagnosis was made was included. Patients less than 2 years of age and those without post-mortem studies also were omitted. A small number of reports could not be

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included because the data were incomplete or the journals were unavailable.^{105-117,141} Abbott,¹¹⁹ using the same criteria, analyzed 200 cases from the time of the earliest report¹⁵¹ in 1791 to 1928. The 104 cases collected since the latter date form the basis of the present review. Unfortunately, some gross and many microscopic observations were lacking in the majority of these reports.

SEX

Coarctation is about four to five times more common in males than in females. The ratio was approximately 5:1 in this series (87:17) and 4:1 in Abbott's series. There is no evident reason for this preponderance.

AGE

In this series, ages ranged from 3 to 76 years. The adult type has been reported in patients from 6 months¹⁵⁹ to 92 years¹⁵⁴ of age. The average age at death was 35.0 years, a figure comparable to Abbott's data (see Table I). According to causes of death, the average ages varied from 27.7 to 47.0 years. Sixty-one per cent of these patients died before or during the fortieth year of life. Considering the fact that Abbott's series included cases reported over a span of 137 years, during which time life expectancy has increased greatly, it is not surprising that she found that 74 per cent of her patients died before or during the fortieth year of life. The percentages of patients in each age decade in this series is quite similar to the corresponding data presented by Abbott. The majority of the deaths from rupture of the aorta or from an intracranial lesion occurred in the second and third decades, from bacterial endocarditis or aortitis in the first five decades, and from congestive failure in the third to fifth decades. Deaths from incidental causes occurred throughout all decades with a peak in the fifth decade.

CAUSES OF DEATH

Seventy-four per cent of these patients died as a result of rupture of the aorta, bacterial endocarditis or aortitis, congestive failure, or an intracranial lesion. The remaining 26 per cent died of causes which may be considered as "incidental." Approximately the same frequencies of the various causes of death were found by Abbott, although the exact percentages are not stated. The only discrepancy of some magnitude is her observation that 29 per cent of patients died of congestive failure and 16 per cent died of bacterial infection of the heart or aorta. This is understandable when one considers the progress in pathologic recognition of congestive failure and bacterial endocarditis and aortitis during the past century or more.

Incidental Causes.—Included in this group were patients with coarctation who died as a result of pneumonia,^{12,33,69,64,95} probable uremia,^{47,51,85,88} carcinoma with bacteremia,⁸² carcinoma,^{13,24} trauma,^{4,6,31,49} postoperatively after major surgery,^{50,60} pulmonary embolism,^{28,34} perforation of a duodenal ulcer,⁵⁷ or acute esophagitis.⁷⁰ Three patients^{5,63,75} died suddenly of coronary artery disease and

TABLE I. DATA PERTAINING TO 104 AUTOPSED CASES OF COARCTATION OF THE AORTA (ADULT TYPE), TWO YEARS OF AGE OR OLDER

CAUSES OF DEATH	NUMBER OF COARCTATION PATIENTS IN EACH AGE DECADE								TOTAL NUMBER OF PATIENTS	% TOTAL DEATHS (THIS SERIES)	% TOTAL DEATHS (ABBOTT'S SERIES)	AVERAGE AGE (THIS SERIES)	AVERAGE AGE (ABBOTT'S SERIES)	BICUSPID AORTIC VALVES	
								NUMBER						% ACCORD-ING TO CAUSE OF DEATH	
	2-10	10-20	20-30	30-40	40-50	50-60	60-70								OVER 70
Incidental	1	3	1	2	10	2	6	2	27	25.9	22.5	47.0	?	8	29.6
Rupture of the aorta	1	8	8	2	3	2	0	0	24	23.1	20.0	27.7	22.2	10	41.7
Bacterial endocarditis or aortitis	3	3	7	5	4	1	0	0	23	22.1	16.0	28.7	?	14	60.9
Congestive failure	0	1	3	5	7	1	1	0	18	18.3	29.0	39.3	?	8	42.1
Intracranial lesion	0	3	4	2	1	1	0	0	11	10.6	12.5	28.0	30.1	4	36.4
Total	5	18	23	16	25	7	7	2	103	100.0	100.0	35.0	33.5	44	42.3
% Total deaths (this series)	4.8	17.5	22.3	15.6	24.3	6.8	6.8	1.9							
% Total deaths (Abbott's series)	4.5	22.5	24.5	22.5	14.0	6.0	5.0	1.0							

Abbott¹¹⁹ estimated the age in 16 of her 200 cases. One case²⁵ in this series was omitted, as the age was given as "adult."

two others^{53,62} died suddenly from unexplained causes. Only 29 per cent of the deaths from incidental causes occurred before or during the fortieth year of life.

Rupture of the Aorta.—Two types of aortic rupture occurred: (1) in the ascending aorta, which was more frequent (19 cases; average age, 30.0 years), and (2) in the descending aorta just distal to the coarctation (5 cases; average age, 19.1 years). No cases of rupture of the area just proximal to the coarctation or of other portions of the thoracic aorta were found. Ruptured mycotic aneurysms were included with the bacterial group rather than in this group. In one instance³ there was an associated syphilitic aneurysm in the ascending aorta some distance above the point of rupture. The ruptured segment of the aorta most commonly was dilated and occasionally was described as unusually thin or "hypoplastic"; it was rarely of smaller diameter than normal.

Patients with rupture of the ascending aorta had the usual symptoms of dissecting aneurysm. Death resulted from rupture of the aneurysm into the pericardial cavity with resulting hemopericardium. In the five cases with rupture distal to the coarctation, the aorta eroded into a bronchus,⁴⁴ into the esophagus,^{7,65} into both,⁸ or into the left pleural cavity.⁶⁷ Rupture almost always was rapidly fatal, although the possibility of survival is indicated by two reports. The first⁴⁶ was a report of a man 62 years of age who suffered rupture of the descending aorta just distal to an extreme coarctation, lived twelve days, and then shot himself. The second¹⁰⁴ was the report of a man 45 years of age with an aneurysm dissecting distally from a moderate coarctation, who died nineteen months later from congestive failure. In the latter case the aneurysmal lumen was endothelialized and contained a canalized thrombus. Recovery from ascending aortic dissection occurs rarely, although no such report is included in this series.

It seems probable that aortic rupture is associated with an abnormal vessel wall. Hypertension was present unless the patient was in shock. No correlation could be found between systolic, diastolic, or pulse pressure levels and the incidence of rupture, when these findings were compared in patients who died of aortic rupture and in patients who died of other causes. In the series of 104 cases, dilation was commonly observed in the aorta, especially in the ascending portion and less commonly in the descending portion. The majority of these dilated areas had not ruptured. It is unfortunate that so few complete microscopic studies of the aorta in regions of rupture and below and above the area of coarctation were described. In general, the media appeared somewhat decreased in thickness and showed varying amounts of necrosis or hyaline degeneration, fibrosis, elastic decrease and fragmentation, basophilic appearance, or cystic change. Atheromatosis was common and the vasa vasorum occasionally exhibited narrowing of lumina by intimal and/or medial thickening. Elastic destruction appeared to be the outstanding lesion. A few reports^{48,55,76} indicated that the various changes were more marked proximal to the coarctation, although the number is too small to justify conclusions. Microscopic study of a significantly large number of cases might clarify the relative importance of congenital thinning and medial changes due to hypertension or other factors, in the production of aortic dilation and rupture in coarctation.

Bacterial Endocarditis.—In the large majority of cases the aortic cusps, very frequently bicuspid, were affected, although in two instances^{40,42} the bacterial vegetations involved only the cusps of the mitral valve. Alpha streptococci were the most frequent infecting organisms. The clinical courses and associated findings were typical of subacute bacterial endocarditis and death resulted in the usual manner. The nature of the valvular destruction usually resulted in marked aortic insufficiency with high pulse pressures, typical murmurs, associated vascular phenomena, and cardiac hypertrophy. There were two cases of aortic vegetations associated with Roger's disease in which bacterial vegetations were present on the interventricular septal defects.^{36,94} Two patients were described as also having syphilitic aortitis (not valvular).^{29,90} Seventy per cent of the deaths from bacterial endocarditis occurred before or during the fortieth year of life; the ages at death ranged from 3 to 57 years and averaged 31.2 years. In fourteen of the seventeen patients with bacterial endocarditis, the involved valves were abnormal, either congenitally bicuspid (aortic) or the site of previous valvulitis, apparently rheumatic. The valves were not described in further detail in the remaining three cases.^{2,41,42} This tendency for bacterial endocarditis to develop on abnormal cusps is illustrated by comparing the incidences of bacterial vegetations on valves described as "normal" (no instance of bacterial endocarditis in thirty-two cases) and on bicuspid or previously damaged valves (fourteen of sixty-two cases; that is, 23 per cent).

Bacterial Aortitis.—Death from this condition, unassociated with bacterial endocarditis, occurred in six patients whose ages varied from 7 to 38 years and averaged 21.7 years. In two instances the vegetations were on the ascending aorta and in the other four, just distal to the area of coarctation. The mechanisms of death were as follows: overwhelming infection,⁷¹ extension to pericardium with acute pericarditis,⁶⁶ rupture into pericardial cavity with hemopericardium,³⁵ hemoperitoneum from rupture of a mycotic mesenteric aneurysm,¹⁰ rupture into the lung,⁵⁶ and uremia with marked embolic glomerulonephritis.⁹ The symptomatology mimicked that of bacterial endocarditis; death usually occurred suddenly. The gross descriptions of these aortas, exclusive of the vegetations, did not differ from those in which aortitis did not occur. A single case of apparent spontaneous recovery from bacterial aortitis has been reported, with progressive calcification of an aneurysmal dilation of the aorta (possibly mycotic), distal to the coarctation.¹⁴⁹ We have seen a man, aged 28 years, with coarctation, positive blood cultures for alpha streptococci, and malaise and fever following tooth extraction, and no diastolic murmur, who appears cured one year after massive penicillin therapy. Recent back pain and an expansile sensation in the region of a recently developed aortic dilation just distal to the coarctation suggest that this patient's bacterial invasion occurred in this site.

Several patients with bacterial endocarditis had an associated bacterial aortitis of the ascending portion⁴⁶ or just distal to the coarctation.^{29,64} Two patients who died of other causes (dissecting aneurysm of the ascending aorta⁹¹ and rupture of an intracranial aneurysm,⁹² both apparently not mycotic) also had bacterial aortitis just below the coarctation; one also had bacterial endocarditis of the mitral valve.

Congestive Failure.—The most striking feature in the patients who died primarily as a result of congestive failure was the high incidence of associated cardiovascular malformations or lesions which, per se, could cause failure. Of nineteen patients with coarctation who died of congestive failure, only the records of one contained no mention of renal disease, chronic valvular disease, coronary artery disease, or some other definite cardiac abnormality. Twelve patients had chronic valvular disease: aortic stenosis^{43,52,103}; aortic stenosis and insufficiency²⁶; aortic insufficiency^{48,77}; aortic valvular disease⁸⁴; aortic and mitral disease^{58,102}; aortic, mitral, and tricuspid stenosis¹; and valvular disease with acute rheumatic carditis.^{22,38} Three additional patients^{87,98,99} had chronic valvular and coronary artery disease. One other patient⁷³ had marked aortic stenosis, coronary artery disease, and arteriolar nephrosclerosis. Another patient, 23 years of age, had extreme coarctation, patent ductus arteriosus, and symptoms suggesting portal cirrhosis for two years. Death occurred six months after a Talma-Morison omentopexy, supposedly from rapidly progressive congestive failure. This patient also had a paroxysmal tachycardia terminally and left bundle branch block.⁸⁹ Still another patient,⁷⁹ 50 years of age, had auricular fibrillation and electrocardiographic abnormalities suggesting myocardial infarction. Death occurred after eight years of progressive heart failure. Microscopic studies were not described in the reports on these last two patients.^{79,89} The only case¹⁰⁴ in which no mention was made of associated cardiovascular factors was that of a man, 45 years of age, who had cardiac failure for about four years. Nineteen months before death, this patient suffered a dissecting aneurysm just distal to the coarctation.

Despite the existence of numerous cardiovascular factors which tended to produce progressive congestive failure, some of these patients did surprisingly well. The patient with marked aortic stenosis, coronary disease, arteriolar nephrosclerosis, and an extreme coarctation had congestive failure for five years before he died at the age of 35 years.⁷³ A 34-year-old woman had a past history of rheumatic fever; she developed the first signs of congestive failure during her only pregnancy, was delivered of a living child by cesarian section, and died six days post partum. The autopsy showed a moderate coarctation and advanced stenosis of the mitral, aortic, and tricuspid valves.¹ Another patient was hospitalized thirty-six times during a period of twelve years because of congestive failure. He died at 68 years of age with marked aortic stenosis and insufficiency, marked coronary arteriosclerosis, diffuse myocardial fibrosis, and complete aortic atresia at the usual site.⁹⁸

Hypertension was present in all but one patient who died from congestive failure in whom the blood pressure was recorded, and all of these patients showed left ventricular hypertrophy, the three largest hearts^{43,79,84} weighing 1,140 (with great vessels), 1,200, and 1,240 grams, respectively. There was no apparent relationship between the duration of failure and the heart weight or degree of coarctation, probably because of associated cardiovascular factors. All six patients in whom the duration of failure appeared to be one year or less had advanced deformity, usually stenosis, of the aortic valve. The only death from congestive failure in a patient under 21 years of age occurred in a 13-year-old

girl who died suddenly with massive congestion.¹⁰³ Her aortic cusps showed extreme thickening and fusion, typically rheumatic; a moderate coarctation was present. A murmur was noticed four days after birth and repeated epistaxes occurred in childhood.

These studies should not be interpreted to indicate that coarctation does not cause congestive failure. Abbott¹¹⁹ cited several outstanding examples of congestive failure in young persons with normal valves; these constituted approximately 3 per cent of her total series. In these patients the absence of other cardiovascular factors is not clearly indicated. It is logical to assume that moderate, extreme, or complete occlusion of the first part of the descending aorta with persistent hypertension would impose an extra burden on cardiac function. This assumption is borne out by a number of studies.^{115-124,134,166} The present study merely indicates that the great majority of these patients did not die of congestive failure until some additional strain was placed on cardiac function. These patients died at an average age of 39.3 years, the range being from 13 to 67 years. The age decades during which most of these patients died were the decades during which most patients with chronic valvular heart disease, without coarctation, die.

Intracranial Lesions.—The majority of these patients died during the age period of 10 to 30 years from subarachnoid hemorrhage due to rupture of an intracranial aneurysm. There were eleven cases of death from intracranial lesions, and these cases were responsible for 10.6 per cent of all deaths in the series. The ages at the time of death ranged from 11 to 54 years, the average being 28.0 years. Three cases of cerebral embolism with bacterial endocarditis^{23,40,41} were included with the endocarditis cases rather than with the intracranial group.

The brain was examined in nine of the eleven cases. Of these nine cases, a ruptured aneurysm was found in five.^{14,17,45,68,92} Two additional patients, 11 years³⁹ and 36 years¹⁰⁰ of age, respectively, had subarachnoid hemorrhages but no ruptured aneurysm was found; the latter patient had one pea-sized aneurysm which had not ruptured. The remaining two cases in which the brain was examined were the two oldest patients in the group with intracranial lesions. One of these was a man, 47 years of age, who had dyspnea for eighteen months and died with symptoms of a cerebral vascular accident. Autopsy studies showed marked cerebral arteriosclerosis but no evidence of hemorrhage or infarction.¹⁰¹ The other patient, a 54-year-old woman, died of cerebral embolism. She had three saccular aortic aneurysms, one in the ascending portion, one in the transverse portion which contained several friable thrombi, and one distal to the coarctation.²⁵ The two patients in whom the brain was not examined were both 22-year-old men; the cause of death was reported as probable intracranial hemorrhage.^{11,21}

It is of interest to speculate on the lack of autopsied cases of cerebral hemorrhage due to cerebral arterial diseases other than aneurysm or bacterial arteritis. In view of the prolonged hypertension which these patients had, and the relationship between hypertension and vascular disease, a cerebral vascular accident

should be a fairly common cause of death in coarctation of the aorta, as it is in the so-called "essential hypertension" group. Undoubtedly such accidents occur, yet no instance could be found in this survey. A possible explanation is that these patients do not live long enough to die of "ordinary" cerebral hemorrhage, despite the fact that hypertension has been present many years, even at their younger ages.

In cases of ruptured aneurysms, one or more unruptured aneurysm may be present.⁶⁸ These aneurysms most commonly involve or are near some branch of the circulus arteriosus (Willis) and generally are considered to be of congenital origin. Most frequently they occur at arterial junctions or bifurcations and have been considered the main cause of so-called "spontaneous" subarachnoid hemorrhage in young persons. Microscopic examination of unruptured aneurysms⁴⁵ showed a deficiency of medial tissue, often with little or no evidence of previous inflammation, which is consistent with the concept of a congenital origin. When rupture had occurred, medial fibrosis and atrophy and elastic splitting were seen. In one such case, the aneurysm apparently had "leaked" two years previously.⁴⁵ In an 18-year-old man who died of a dissecting aortic aneurysm, there had been a subarachnoid hemorrhage thirteen months before death. The aneurysm of the left middle cerebral artery was surrounded by fibrous tissue with evidence of old hemorrhage and showed "elastic tissue changes like those in the aorta."²⁷ In another patient,⁷⁹ there was a history of a cerebral vascular accident at the age of 38, twelve years before death. The brain was not examined.

As pressure dynamics probably have an important role in the actual rupture of vessels, it was interesting to find that systolic, diastolic, and pulse pressures tended to be somewhat higher in patients who died of intracranial lesions. However, this observation is difficult to evaluate because of the introduced factor of increased intracranial pressure. The same pressure elevations were not noted in patients who died of rupture of the aorta.

Another cause for aneurysmal dilation of an intracranial artery, particularly a vertebral branch, may be the tremendous collateral arterial development which is so common in coarctation. The vertebral arteries usually arise directly from the thyrocervical trunks of the subclavian arteries. Two cases of vertebral arterial aneurysms have been reported, but in neither case was there rupture of the vertebral aneurysm.^{16,92} In the first of these two cases the vertebral arterial dilation was sufficient to produce pressure atrophy of the adjacent left cerebellar hemisphere, so that perhaps cerebellar pressure symptoms might be added to the list of clinical features of coarctation which are dependent on the extensive collateral arterial development.

In cases of coarctation in which death was not the result of intracranial disease, several incidental cerebral lesions were reported: marked arteriosclerosis with old hemorrhage⁷⁵ or encephalomalacia^{24,32} and meningitis associated with bacterial endocarditis.³⁰

CARDIAC AND AORTIC CHANGES

Left Ventricular Hypertrophy.—Hypertrophy of the left ventricle occurred in all cases, with two possible exceptions. These were in women, each of whom had a moderate coarctation. One patient,⁴⁶ 31 years of age, died of bacterial endocarditis; the heart weighed 330 grams. The other patient⁶⁰ died of an incidental cause at the age of 69 years, and the heart weighed 290 grams. It was difficult to determine to what extent the hypertrophy resulted solely from coarctation. Sixteen reports, in which heart weights and degrees of coarctation were included, indicated an absence of other cardiovascular factors which might cause hypertrophy. These patients were from 7 to 76 years of age. Their hearts weighed from 200 grams (age, 7 years) and 300 grams (age, 16½ years) to 525 grams (age, 25 years). The average weight was 416 grams in the thirteen patients over 20 years of age. No relationship was indicated between the heart weights and the degrees of coarctation in these cases. The reported gross and microscopic studies in all the cases showed no findings of unusual significance aside from the aortic changes and valvular lesions previously mentioned and congenital lesions.

Bicuspid Aortic Valves.—By far the commonest associated congenital lesion was a bicuspid aortic valve. This fact was stressed by Abbott,¹¹⁹ who found an incidence of 23.5 per cent congenital bicuspid aortic valves in her series. In 50 per cent of the patients of her series with this congenital lesion, rupture of the aorta occurred. She also found that coarctation was a common congenital lesion accompanying this anomaly.¹

The distinction between congenital and acquired bicuspid valves may be difficult at times. The criteria advanced by Lewis and Grant¹⁴⁵ and used by Abbott^{1,119} were reviewed and extended quite recently.^{141,142} Microscopic studies of bicuspid aortic valves very rarely were reported in this series of 104 cases that we are analyzing; in ten instances, the presence or absence of this anomaly was not mentioned.^{2,11,13,17,24,42,49,59,64,82} Assuming that these ten patients did not have bicuspid aortic valves, there still were forty-four patients in whom descriptions indicated that bicuspid aortic valves, apparently of the congenital type, were present, an incidence of 42.3 per cent. There were three additional cases in which the bicuspid aortic valves apparently were of acquired origin.^{35,54,84} This incidence is somewhat greater than that reported by Abbott.¹¹⁹ The incidence of bicuspid valves was particularly high (60.9 per cent) in those patients who died of bacterial endocarditis or aortitis. On further study, the incidence of bicuspid valves in the group with bacterial aortitis (unassociated with bacterial endocarditis) was no higher than in any other group (33.3 per cent), but the incidence in the bacterial endocarditis series was significantly greater (70.6 per cent). Of seventeen patients with coarctation and associated bacterial endocarditis, fifteen had bacterial vegetations upon the aortic cusps. In eleven of the fifteen patients the cusps were congenitally bicuspid. In the other two patients with endocarditis, the mitral rather than the aortic cusps were involved.

This observation that nearly three-fourths of the patients with coarctation and bacterial endocarditis had bicuspid aortic valves raises the question whether

the presence of coarctation increases the frequency of development of bacterial infection on these valves. The incidence of bacterial endocarditis on bicuspid aortic valves not associated with other congenital cardiovascular lesions has been stated to be approximately 40 per cent,¹ while in this series the same incidence in cases of bicuspid aortic valves with coarctation was 27.3 per cent. From these data it does not seem likely that coarctation, per se, increases the incidence of bacterial endocarditis.

The main clinical importance of bicuspid valves seems to be that they are frequent sites for the development of bacterial infection. The suggestion has been made that the development of bacterial endocarditis on bicuspid valves is more dependent on previous rheumatic valvulitis than on the presence of the congenital anomaly itself.^{141,142} Two patients had bacterial vegetations on mitral leaflets which appeared to have been damaged previously, while the aortic valves, one of which was bicuspid,⁴⁰ appeared to be undamaged. Also, of six patients with bacterial aortitis, five had undamaged heart valves (two of these patients had bicuspid aortic valves) and the other had marked calcific aortic stenosis. However, previous rheumatic damage does not readily explain bacterial invasion of the aorta, of a patent ductus arteriosus, or of an interventricular septal defect. Thus, the exact role of congenital bicuspid valves in the pathogenesis of superimposed bacterial endocarditis is not clear.

Recent studies^{137,153} suggest that rheumatic carditis is much more frequent than is realized generally, with gross lesions often of slight extent. Descriptions of the bicuspid aortic valves in this series indicated that previous rheumatic valvulitis was more frequent than bacterial endocarditis. Of the forty-four examples of coarctation with congenital bicuspid aortic valves, the valves were involved by previous valvulitis, apparently rheumatic, in 43 per cent and by bacterial endocarditis in 27 per cent, and in 30 per cent the valves appeared grossly normal. While these findings may seem to suggest that this congenital anomaly is more vulnerable to rheumatic inflammation than are normal aortic cusps, this postulate lacks proof. It is our impression that bicuspid aortic valves commonly accompany coarctation, frequently are the site of rheumatic valvulitis, and are liable to bacterial invasion either because they are congenitally bicuspid or because they have been affected previously by rheumatic inflammation of varying extent.

Associated Rheumatic Heart Disease.—A study was made of the incidence of rheumatic heart disease in these cases. Of ninety-three instances in which fairly complete valvular descriptions were given, there were four cases of mitral stenosis, fifteen cases of "typically rheumatic" aortic or mitral valvular disease (exclusive of mitral stenosis), ten cases of "slight thickening" of aortic or mitral valves, and eleven cases of "calcific aortic stenosis," making a total of forty cases, that is, 43 per cent, with valvular disease. Although the incidence of typically rheumatic valvular disease (nineteen cases or 20.4 per cent) is increased over the same incidence (7.7 per cent) in a series of 4,437 autopsies at the Peter Bent Brigham Hospital,¹⁶² this increase is probably more apparent than real and most likely depends on the variability of rheumatic criteria. Furthermore, mitral

stenosis, unquestionably rheumatic in genesis, was found in approximately the same frequency in this series (4.3 per cent) as in the series of 4,437 autopsies (5.1 per cent). Abbott,¹¹⁸ in her study of 1,000 cases of congenital cardiac disease, found 222 cases of "acquired valvular disease." One may suspect that there is an increased incidence of associated rheumatic heart disease in this group of cases of coarctation but the evidence is not conclusive.

Other Congenital Anomalies.—These included cases suggesting some combination of adult and infantile types of constriction,^{7,15,27,48,69,78,83,85,88,89,94,98,101} patent ductus arteriosus,^{20,30,89} interventricular septal defects,^{36,94} patent but competent foramen ovale,^{51,54} and probably⁴² subaortic stenosis,^{80,83} anomalous origin of aortic arch vessels,^{6,27,31,34,47,57,64,71} bifid coronary artery,⁵⁴ unequal width of aortic cusps,^{15,80} accessory mitral cusps,²⁷ minor anomalous aortic cusp insertions,⁹¹ hypoplastic descending aorta,^{24,26,36,44,59,74,80,102} hypoplastic abdominal aorta,^{9,21,22,41,42,89,92} hypoplastic descending and abdominal aorta,^{8,17,48} considerably thickened aorta just distal to coarctation,⁷⁰ and hypoplastic ascending aorta.^{91,102} There were also occasional minor anomalies affecting other parts of the body than the cardiovascular system.

Degree of Coarctation.—Following the method of Abbott,¹¹⁹ these cases were classified into three degrees of stenosis, according to the size of the lumen through the coarctated area: *moderate*, 0.5 cm. or somewhat more; *extreme*, less than 0.5 cm.; and *complete*, atresia (that is, complete occlusion). In most of the extreme cases only a hair, bristle, or fine sound could be passed through the lumen. The frequencies of these types of stenosis in comparison to Abbott's (in parentheses) were as follows: moderate, 33.3 per cent (22.5 per cent); extreme, 41.5 per cent (54 per cent); and complete, 25.2 per cent (23.5 per cent). In five cases the degree of coarctation was not indicated. There was no evident relationship between the degree of coarctation and the ages or causes of death, levels of blood pressure, incidence of congestive failure, or cardiac weight. On the other hand, there was an apparent relationship between the degree of coarctation and the extent of collateral arterial development demonstrated at autopsy. In twenty-one patients in whom these collateral anastomoses were very marked, no examples of moderate coarctation were found, the degree of coarctation being equally divided between the extreme and complete groups. On the contrary, all six patients in whom no collateral circulation was demonstrable at autopsy had moderate coarctation^{9,10,46,78,85,91}; the ages ranged from 8 to 31 years.

Probably because of its relationship to collateral arterial development with resultant rib erosion, the degree of coarctation appeared to be related to the incidence of ante-mortem diagnosis. In eighty-seven cases it was possible to ascertain definitely whether ante-mortem diagnosis had been made. There were forty-two cases in which the diagnosis had been made; the degree of coarctation was not stated in two. There were forty-five cases in which diagnosis was not made; the degree of coarctation was not stated in one. Of the diagnosed cases, 25 per cent had moderate and 35 per cent had complete coarctations,

while of the undiagnosed cases, 48 per cent had moderate, and but 9 per cent had complete coarctations. Ante-mortem diagnoses were made in 40 per cent of the entire series of cases, in contrast to 14 per cent in Abbott's series.

CLINICAL FEATURES

Murmurs.—The murmur in coarctation of the aorta is systolic in time and is heard over the precordial region, especially at the base, and often in the back between the scapulas or alongside the lower dorsal spine. Its intensity is moderate to extremely loud. The loudest types of murmurs are accompanied by a thrill and are widely transmitted to the neck and elsewhere. Transmission of murmurs has been shown to be dependent primarily on intensity and not on direction of blood flow.¹⁴⁴ However, more diagnostic of coarctation than the finding of a systolic murmur in the back is the observation that this murmur accompanies a murmur of only moderate intensity anteriorly, or, rarely, a murmur of less intensity anteriorly. For example, one may suspect coarctation if a murmur is heard between the scapulas, and yet the murmur heard anteriorly is but Grade 2 in intensity. In one case¹⁷ the murmur in the back was described as louder than that over the precordium, and another report²⁴ described a murmur which was heard only posteriorly. Systolic murmurs were heard in all sixty-six cases in which mention was made of physical examination of the heart; in twenty-three of these it was stated that a murmur was heard posteriorly. We, in our limited experience, have never seen an instance in which a systolic murmur was entirely absent or was louder in the back than over the precordium.

One wonders about the mechanism of production of this systolic murmur. The fact that it is usually loudest over the precordium would rule against the possibility of the collateral channels themselves giving rise to the bruit; the finding of a systolic murmur over an enlarged intercostal or scapular artery may as well be due to murmur transmission. From analogy with the production of murmurs in chronic valvular heart disease, one reasonably could explain the systolic murmur on the basis of stenosis of the aorta, this stenosis being more distally situated than that in chronic valvular disease. In no case of complete aortic atresia in which a systolic murmur was noted was there proof that the coarctation alone produced the murmur,^{13,17,48,83,86,87,95,98} since some other condition such as valvular or subaortic stenosis was present. One possible exception was the case of a 13-year-old boy who died of a ruptured intracranial aneurysm.⁶⁸ This patient had a rough precordial systolic murmur, maximal in the third left interspace. In addition to complete aortic atresia, he had a bicuspid aortic valve, one cusp of which was much larger than the other, with a large median raphe. There was also patency of the ductus arteriosus for one-half its length on the pulmonary side. A case of interest was that of a man, 50 years of age, with complete aortic atresia, who died of bacterial endocarditis of the aortic valve. This patient was reported to have had only a diastolic murmur.⁹⁰ In one patient in whom the degree of coarctation was not mentioned but in whom collateral circulation was clinically evident, the statement was made that no bruit was heard over the anterior or posterior thorax,⁸² and in another case of

complete atresia²⁸ no bruit was reported. However, these observations do not prove that stenosis of the aorta is the only mechanism responsible for the murmur.

A diastolic murmur is not found in uncomplicated coarctation of the aorta. When present (in twenty cases in the series) it was associated with aortic valvular deformity including bacterial endocarditis, or patency of the ductus arteriosus, except in three instances, in which the valvular appearance was not described or the patient was in shock.^{11,14,91}

Collateral Circulation.—The extensive collateral circulation which develops in coarctation has been thoroughly diagrammed¹⁴³ and can be well visualized by post-mortem x-ray study after injection of radiopaque material.^{17,100} The degree of collateral dilation, as well as the exact routes involved, determines, to a large extent, the signs and symptoms in an individual case.

Visible pulsation, and sometimes tortuous vessels, may be present in intercostal, axillary, suprasternal, carotid, deltoid, brachial, supraclavicular, supra-scapular, subscapular, interscapular, or superficial epigastric regions. Rarely, aneurysmal dilation of a vessel may be palpated.⁸ In one case an aneurysm of the innominate artery was suspected.¹⁰² Flushing, headaches, buzzing, a sensation of warmth or fullness in the head or upper extremities, a pounding sensation, nodding of the head, or epistaxis may be noted; these subjective sensations are sometimes exacerbated by bending or stooping. These symptoms, when combined with those indicating decreased arterial pressure in the lower extremities, particularly suggest coarctation.

Differences of the Circulation in the Two Upper Extremities.—Uncommonly there may be a marked difference of circulation of the two upper extremities. This usually consists of a decreased circulation in the left arm¹³³ because of encroachment upon the orifice of the left subclavian artery by the coarctation, which results in partial occlusion of this vessel. This extremity may then show decreased warmth and less redness, a lower blood pressure, a smaller or even absent pulse, and occasionally numbness or tingling. Variations of circulation of the two upper extremities have been discussed in some detail.¹⁴⁰ The opposite situation, with decreased circulation of the right arm, has been described⁶⁴ and apparently is due to a congenitally small right subclavian artery.

Results of Increased Arterial Supply to the Upper Part of the Body.—Other results of the increased arterial supply to the upper part of the body may be noted, such as relative overdevelopment of tissues (particularly in contrast to the lower extremities), full, tortuous retinal arteries,¹³⁸ enlargement of the mandibular arteries with prognathism, and relative increase in premaxillary dental pulp.¹⁴⁷ The possibility of symptoms from vertebral artery dilation already has been discussed in the case with unilateral cerebellar atrophy.¹⁶ Another patient¹³⁶ showed transverse myelitis which apparently resulted from enlargement of the spinal artery. Mental aberration with repeated transient paralyses has been reported.⁴⁰ The thyroid arteries may be enlarged and one author,⁸⁹ who found that two of his patients (autopsies not reported) had symptoms of hyperthyroid-

ism with elevated basal metabolic rates (to plus 42 per cent), considered that increased blood supply might be a factor in thyroid overactivity. A few similar cases have been reported.^{13,23,121,126,134,146} These reports do not establish the existence of hyperthyroidism either because there were present factors which per se might raise the metabolic rate or because no pathologic studies of the thyroid gland were made. For example, a woman, 30 years of age, had exophthalmos, throbbing neck vessels, warm hands with cold feet, tremor, and an enlarged thyroid gland. She developed alpha streptococcic bacteremia, with fever, pallor, clubbing, petechiae, a palpable spleen with infarction, and hematuria, and died of cerebral embolism from bacterial endocarditis.²³ The basal metabolic rate was not determined and the thyroid gland was not examined pathologically.

Radiologic Findings.—Radiologic demonstration of *rib erosion*, or notching of the lower borders of ribs, depends on the development of collateral arterial circulation. Since this finding was described,^{75,152} ante-mortem diagnosis probably has been made most frequently by the radiologist. In only forty-three cases in this series was its presence or absence noted. Rib erosion was present in 75 per cent of these forty-three cases, only 10 per cent of which had moderate coarctations. On the other hand, 80 per cent of the cases without rib erosion had moderate coarctations. This important sign has been thought to depend somewhat on age, for it usually has not been seen until the second decade or at least the end of the first decade of life.⁴¹ In one case in this series it was demonstrated in an 11-year-old boy.³⁹ Other reports indicate that rib erosion occurred at a slightly earlier age.^{123,163} One instance of rib erosion demonstrated at the age of 9 months¹⁴⁸ suggests that further studies are indicated.

Other radiologic findings may include absence or reduction in size of the aortic knob, especially striking with hypertension which ordinarily accentuates this portion of the aorta; dilation of the ascending aorta; lack of prominence of the descending aorta; or a narrowing or defect of the descending aorta at the level of the pulmonary artery. The latter observation established an ante-mortem diagnosis of coarctation in a 31-year-old woman who had no hypertension of the upper extremities or hypotension of the lower extremities and no rib erosion.⁴⁶ This patient had precordial systolic and diastolic murmurs and a vigorous supra-sternal systolic pulsation and died of bacterial endocarditis of a bicuspid aortic valve. There was a moderate coarctation. To this list of radiographic observations should be added the demonstration of cardiac hypertrophy and the visualization of the coarctation by intravascular injection of diodrast.^{132,155}

Decreased Arterial Blood Pressure in the Lower Extremities.—This finding may be the first clue that coarctation exists, particularly when it is accompanied by an increased arterial circulation in the upper extremities with hypertension. Routine palpation of the femoral pulses, especially in young persons with hypertension, frequently establishes the diagnosis. The pulsations in the abdominal aorta, popliteal, tibial, or dorsalis pedis arteries, as well as the femoral, may be reduced or absent. In coarctation, the pulse in the lower extremities has been shown to occur later than in the radial arteries.^{61-63,170} The blood pressure in the

lower extremities may be low or unobtainable instead of being approximately equal to, or greater than, that in the upper extremities.

In this series, symptoms due to lowering of the arterial pressure in the lower extremities included coldness, pallor, numbness, or pain in the legs, intermittent claudication, and weakness. Whenever hypotension of the lower extremities was mentioned, it was present, with the one exception previously cited⁴⁶ in which the diagnosis was made solely by the x-ray findings. All degrees of coarctation were noted. The youngest patient with decreased femoral pulsations studied post mortem was a 5-year-old girl who had a moderate coarctation and severe renal disease. The brachial arterial pressures were as high as 220/190, while the highest systolic pressure in the lower extremities was 125 mm. Hg.⁸⁸ This case illustrates that the difference between the pressures in the upper and lower extremity is probably more important than the actual pressures.

Hypertension.—Increased pressure in the upper extremities was present in almost all of the seventy-four patients in whom pressures were recorded. There were only five patients in whom an approximately normal brachial pressure was reported; insufficient data were presented in three patients.^{2,58,95} One had moderate coarctation without other signs,⁴⁶ and one had auricular fibrillation.⁴¹ Little significance can be attached to single blood pressure observations, as evidenced by a case in which the reading was 122/80 at one time and 180/85 at another time.²⁹ Variations between the pressures in the two arms have been discussed previously.¹⁴⁰

The pathogenesis of this hypertension has been the subject of speculation.^{124,125,129,130,150,157,158,164,165} Two mechanisms have been suggested. First, the increased pressure may be the proximal result of aortic occlusion, and, second, the constriction in the descending aorta may act similar to the Goldblatt clamp and produce a hemodynamic renal change. In this series, the brachial arterial pressures most commonly showed moderate elevation of the systolic level to approximately 160 to 180 mm.; the diastolic levels often did not rise above 90 millimeters. This pressure range is the type considered more typical of resistance in the larger arteries, in contrast to the higher diastolic levels with relatively narrow pulse pressures which are thought to indicate arteriolar resistance. Experimental renal hypertension generally is of the latter type and should be present in all parts of the body and not restricted to the upper extremities. Most patients showed lowering of both systolic and diastolic levels in the lower extremities; only two cases were reported in this series in which one or both pressures were higher in the lower extremities.^{81,82} The whole question is complicated by the complexity of the pathogenesis of hypertension and by the fact that some cases in this series may have had renal disease of some magnitude.

Microscopic examinations of arterioles proximal and distal to coarctations, both by biopsy¹³¹ and at autopsy,⁹⁰ have appeared to show no significant differences, although more marked sclerosis in vessels in the arterial distribution proximal to the coarctation was described in one case.¹²⁸ There were insignificant differences in mean arterial pressures in relation to the various degrees of coarctation.

Many patients had few symptoms with the long-standing hypertension. One patient had hypertension at the age of 10 years and was asymptomatic at the age of 33 years, when the blood pressure was 220/110.¹⁶⁴ A second report indicated a nine-year asymptomatic span though hypertension existed from the age of 12 to the age of 21 years.¹²¹ Another patient had a normal blood pressure recorded at 15 years; at 18 years the systolic level was 180 mm., and at 23 years the pressure reached 166/106. The hypertension produced no symptoms.¹⁶¹

One feature of importance in the diagnosis of coarctation needs further investigation, and that is the earliest age at which hypertension may be found. Recently, a brachial systolic arterial pressure of 180 mm. has been observed in a 9-month-old infant with coarctation.¹⁴⁸ Otherwise, the earliest recorded ages at which hypertension was observed appeared to be from 3¹⁵⁶ to 5 years.^{88,169} Even at these early ages there was left ventricular hypertrophy. One of the 5-year-old patients also had renal disease.⁸⁸

SUMMARY AND CONCLUSIONS

A series of 104 autopsied cases of moderate, extreme, or complete degrees of the "adult" type of coarctation of the aorta in patients 2 years of age or older, which have been reported since Abbott's review in 1928, has been reviewed. As a result of this study, the following conclusions are presented:

1. Although coarctation occasionally was compatible with long life, at least 61 per cent of the patients died before or during their fortieth year of life, the average age at death being 35.0 years. The lesion was more common in males.

2. The causes of death and their frequencies were as follows: incidental causes, 26 per cent; rupture of the aorta (most commonly the ascending portion), 23 per cent; bacterial endocarditis or aortitis, 22 per cent; congestive failure, 18 per cent; and intracranial lesion (exclusive of embolism from bacterial endocarditis), 11 per cent.

3. Rupture of the aorta or an intracranial lesion accounted for one-third of all deaths. These accidents occurred mainly in the second and third decades of life. The commonest cause of an intracranial lesion was rupture of an arterial aneurysm, probably congenital, which produced subarachnoid hemorrhage. Survival rarely occurred after either type of rupture.

4. Bacterial endocarditis or aortitis occurred throughout the first five decades of life, most commonly was due to alpha streptococci, and most often (61 per cent) was associated with a bicuspid aortic valve, apparently congenital. Bacterial aortitis was found just distal to the coarctation or in the ascending aorta.

5. Congestive failure was common, but almost all patients who died of this cause had evidence of additional cardiovascular burdens, chiefly marked chronic valvular disease. Despite such handicaps, these patients sometimes lived for surprisingly long periods. Their ages at death corresponded to the ages at death of patients dying from valvular disease with congestive failure.

6. Bicuspid aortic valves were by far the commonest congenital anomaly associated with coarctation. This anomaly was present in 42 per cent of the

cases in this series, particularly in cases with bacterial endocarditis (71 per cent). They frequently appeared to have been the site of previous rheumatic inflammation.

7. Cardiac hypertrophy was the rule. Dilation of the aorta was very common, especially in the ascending aorta, and occasionally proximal or distal to the coarctation.

8. The degree of coarctation appeared to be related to the extent of collateral arterial development and the frequency of ante-mortem diagnosis, which was 40 per cent in this series, in contrast to 14 per cent in Abbott's series. The various signs and symptoms which apparently depend on this collateral circulation are discussed.

9. A systolic murmur of moderate intensity (Grade 2 to 3) occurs in coarctation. It is present characteristically over the upper precordium and in the left interscapular region and is generally almost as loud in the back as anteriorly. Certain observations are presented which suggest that this systolic murmur is due mainly to stenosis of the aorta at the site of the coarctation. A diastolic murmur was not noted in uncomplicated coarctation; when present, it indicated an additional aortic, or less commonly, mitral, lesion, or associated patency of the ductus arteriosus.

10. The cardinal features of coarctation include (a) *hypertension* of the upper extremities (frequently not marked), (b) *lower blood pressure* of the legs (such as absent femoral pulses), (c) *collateral arterial anastomoses* (with *rib erosion* by x-ray), (d) the *systolic murmur* (which may be noted shortly after birth), and (e) *cardiac hypertrophy*.

11. Coarctation of the aorta, although not common, should be diagnosed as early as possible, for it is likely that surgery would be more feasible at that time than later when the aortic wall has become thinned and dilated. When resection of the area of coarctation with anastomosis of the cut ends of the aorta is not feasible, surgical treatment of the associated hypertension may be of value in certain cases, perhaps in patients beyond 15 to 20 years of age. This procedure has been performed in a small series of patients to date.¹⁶⁸ The use of artificial vascular channels may increase the number of future cures of coarctation. The frequent finding in this study of congenital intracranial aneurysms and bicuspid aortic valves, both of which lead to fatal complications, militates somewhat against the otherwise hopeful expectations from surgery. On the other hand, surgery affords the only possible cure of this condition.

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THE TREATMENT OF SHOCK ACCOMPANYING MYOCARDIAL INFARCTION

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THE shock picture in acute myocardial infarction has been a recognized clinical entity since Herrick's¹ classic description in 1912. Experimentally however, occlusion of coronary arteries has failed to produce the frank vascular collapse seen so often clinically. Von Bezold,² in 1867, reported a sharp fall in arterial blood pressure in rabbits after compression of the coronary vessels and several years later Michaelis³ noted comparable changes. In 1930, Sutton and Lueth⁴ observed an immediate drop of 30 to 50 mm. of mercury in the arterial pressure of dogs after partial coronary compression. Condorelli⁵ made similar observations following coronary ligation. Feil, Katz, Moore, and Scott,⁶ on the other hand, found little or no significant change except where an additional factor such as some arrhythmia supervened. Lowe⁷ injected phenol into the myocardium and found that even extensive myocardial damage so produced caused no change in the blood pressure. Gross, Mendlowitz, and Schauer⁸⁻¹¹ have recently investigated the problem under a variety of conditions and have concluded that there is no immediate fall in blood pressure following coronary ligation, but they report a drop which becomes conspicuous after twenty-four hours and persists for about one week. The diminution in cardiac output occurring immediately after ligation is thought to be accompanied by a compensatory peripheral vasoconstriction which serves to maintain the blood pressure temporarily. At the end of twenty-four hours the vasoconstriction decreases, thus permitting hypotension to develop.

Clinically, a different situation prevails. The high incidence of shock or a shocklike state following coronary thrombosis is generally acknowledged. Master, Dack, and Jaffe¹² found, in a series of 135 cases of coronary thrombosis, that manifestations of shock were present in approximately 50 per cent. These manifestations included a precipitous fall in blood pressure, collapse, cold extremities, moist, clammy skin, grayish pallor, and unconsciousness. There is disagreement as to whether these clinical findings represent a true peripheral vascular collapse or the sudden development of cardiac insufficiency. Certainly the described shock picture is in marked contrast to the dyspnea, pulmonary congestion, venous engorgement, and edema found in congestive failure.

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Harrison¹³ has pointed out that a shock picture resembling peripheral vascular collapse may occur in "acute forward heart failure." This is ascribed to a decrease in blood supply to the tissues, resulting from the inability of the heart to maintain its normal output. Fishberg¹⁴ and Stead and Ebert¹⁵ maintain that this is the responsible mechanism following myocardial infarction and have applied to it the term "cardiac shock"; however, as Harrison has noted, in "acute forward failure" due to the tachycardias, Adams-Stokes syncope, etc., the peripheral veins are usually distended, while following infarction they are generally collapsed. Harrison¹³ and Master and his associates¹² suggest as an explanation of this critically important difference that a reflex nervous mechanism initiated by infarction induces peripheral collapse. The work of Condorelli,⁵ Michaelis,³ and Sutton and Lueth,⁴ who found that the drop in blood pressure following coronary ligation could be prevented by previous denervation of the heart, tends to substantiate this view.

Diminished venous return to the heart occurs invariably in all forms of peripheral circulatory failure. This concept, originally introduced and supported by the work of Henderson,¹⁶ has been said by Wiggers¹⁷ to be "the keystone of all modern conceptions of shock." It therefore becomes important to evaluate the shock picture in coronary thrombosis in terms of this concept. The studies of Fishberg, Hitzig, and King¹⁸ on a series of fifty-nine cases of coronary thrombosis indicated that the development of shock was usually associated with a marked decrease in venous return to the heart. In these patients there was generally a diminution in circulating blood volume, the venous pressure was lower than normal, and there was no significant increase in the circulation time through the lungs. It thus becomes difficult to place the collapse associated with myocardial infarction in any other category than that of shock. This can be described, according to Atchley,^{19,20} as "medical shock" and is therefore akin to the circulatory collapse observed in such conditions as diabetic coma, pneumonia, and typhoid fever. This entity is distinct from that encountered in congestive heart failure. It is not paradoxical, however, to note that even in the presence of severe peripheral collapse, evidence of venous and pulmonary engorgement may appear. The myocardial damage may so reduce cardiac efficiency that the classic picture of congestive failure can develop and be superimposed on the shock. This is particularly likely to occur in the presence of pre-existing cardiac damage.¹² The height of the venous pressure will depend, therefore, on whether myocardial failure or shock predominates.

The prognosis of the patient with coronary thrombosis in shock is ominous. Master and co-workers,²¹ Fishberg,²² and Levine²³ state that a systolic pressure of 80 mm. or less is generally of very grave significance. Although recoveries take place, they are uncommon.²⁴

Wiggers¹⁷ has shown in experimental hemorrhagic shock that if mean arterial pressures of from 35 to 80 mm. are allowed to persist for more than a few minutes or several hours, depending upon the severity of the hypotension, a further abrupt drop occurs and death results despite replacement of the blood. This indicates that the persistence of such low blood pressures will usually precipitate

irreversible shock. It is not entirely clear what these precipitating mechanisms are, but failure of both the heart and the vasomotor center appear to be implicated. In the problem under consideration the former is of special interest. There is some evidence that during shock the myocardium is depressed.¹⁷ Wiggers¹⁷ believes that myocardial depression may be assumed a priori in prolonged hypotension, since there is obviously a significant decrease in coronary blood flow. It seems likely, therefore, that in the presence of a myocardial infarction prolonged hypotension resulting in additional myocardial anoxia is of particularly serious import.

Specific antishock therapy in coronary thrombosis is generally not mentioned in the literature or mentioned only to be discouraged.²⁵⁻²⁷ Most authors feel that the use of plasma and blood is contraindicated in the presence of myocardial injury. Gilbert²⁸ states that in shock following infarction, "Blood pressure should be left where it is and not tampered with," and Stroud²⁹ suggests that "perhaps a drop in blood pressure is an effort on the body's part to protect the myocardium." The very high mortality among such patients in shock militates against this viewpoint. Although cardiac failure is ever imminent and even rather frequent¹² in those surviving for any appreciable length of time, it would appear that treatment of the shock might be indicated in the absence of evident signs of failure and that the problem of cardiac failure should be made a matter of concern only after the critical shock period is safely past. Levine,³⁰ in the most recent edition of his textbook, mentions a patient with coronary thrombosis in profound collapse who was given an infusion of 250 c.c. of plasma which was repeated four hours later with great benefit.

An unusual combination of clinical conditions led to the use of vigorous antishock therapy in a patient with coronary thrombosis, with apparently excellent results.

CASE REPORT

The patient was a 65-year-old male singer admitted to Billings Hospital on Jan. 30, 1946, complaining of exertional dyspnea for fifteen years, orthopnea and swollen legs for two months, and a productive cough for one week. For twenty-five years he had been treated intermittently for duodenal ulcer which responded to dietary management and alkalis. Six months before admission roentgen examination revealed complete healing of the ulcer. Recurrent attacks of back pain had been explained on the basis of x-ray evidence of osteoarthritis of the thoracic spine.

Physical Examination.—The patient was dyspneic, orthopneic, and mildly cyanotic. The fundi showed increased tortuosity of the vessels and arteriovenous nicking. A few fine, moist râles were present at both lung bases. The apex impulse was palpated in the sixth intercostal space 11 cm. from the midsternal line. There were no thrills. The heart sounds were regular and of fairly good quality; A_2 was greater than P_2 . A blowing systolic murmur of moderate intensity was heard over the entire precordium. The blood pressure was 180/108. Pulse rate was 104 per minute. The liver edge was palpable 5 cm. below the right costal margin. There was pitting edema of both lower extremities.

Laboratory Examination.—The hemoglobin was 14 Gm. per 100 c.c.; the red blood cells, 4.8 million per cubic millimeter; and the white blood cells, 13,100 per cubic millimeter. The differential count was normal. The urine was negative except for 200 white blood cells per high-power field in a centrifuged specimen.

X-ray examination showed a heart that was 33 per cent oversized with a hypertensive configuration. There was mild chronic passive congestion of the lungs. Osteoarthritis of the thoracic and lumbar vertebrae was also present.

Hospital Course.—On standard therapy, including digitalization, the patient improved rapidly. One week after admission he passed a stool containing dark red blood. The hemoglobin at this time was 12.8 Gm. per 100 cubic centimeters. Five hundred cubic centimeters of whole blood were given slowly the following day. During this episode the patient developed symptoms of duodenal obstruction and was placed on dietary management. All symptoms abated within one week. Gastrointestinal x-rays showed a duodenal ulcer with a moderate degree of obstruction. At this time there was no evidence of heart failure: the dyspnea, orthopnea, râles, and edema had disappeared. Four weeks after admission the patient complained of rather severe pain in the upper back similar to the pains ascribed to arthritis on previous occasions. This was unrelieved by aspirin and codeine. Physical examination was unchanged. During the following six hours the pain became progressively more severe and spread to the left anterior chest. The patient then arose from bed, vomited a small quantity of bile-stained gastric contents, and fell to the floor.

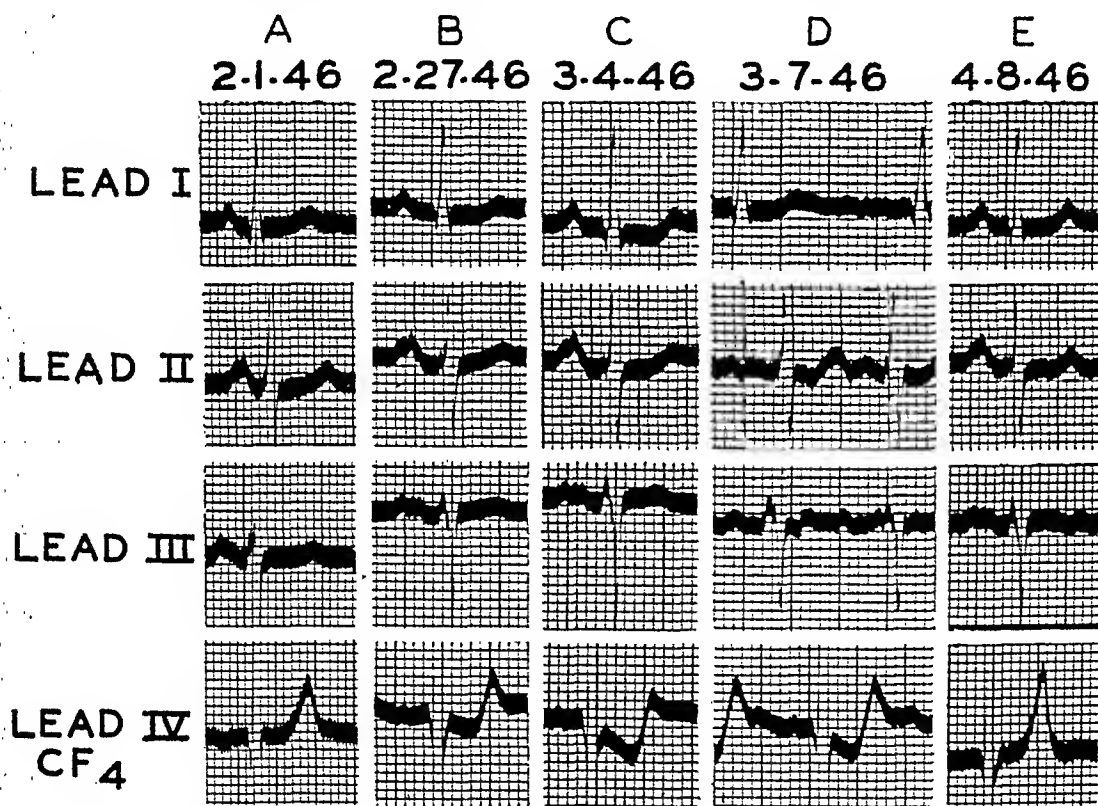


Fig. 1.—Serial electrocardiograms taken on patient B. W. A, On admission to the hospital suffering from heart failure. B, The day following onset of coronary thrombosis. C, D, and E, Subsequent tracings showing the development of the infarction pattern.

On examination he was semicomatose, cold, clammy, and cyanotic. Respirations were rapid and shallow. The pulse was imperceptible and no heart tones could be heard. All visible veins were collapsed. Blood pressure was unobtainable. The abdomen was soft. Rectal examination was normal. Although the patient's condition could have been attributed to either coronary occlusion or concealed gastrointestinal hemorrhage, the history of severe pain in the chest and back favored the diagnosis of myocardial infarction. Because the patient appeared moribund, vigorous treatment for shock was instituted. He was placed in the Trendelenburg position and needles

were inserted with difficulty into two of the collapsed peripheral veins. During the next forty minutes, 1,800 c.c. of plasma and 400 c.c. of whole blood were administered. The blood pressure, which had been unobtainable during this time, suddenly rose to 140/105. Plasma and blood were immediately discontinued, and the patient was closely observed for signs and symptoms of congestive heart failure. No dyspnea, râles, or edema developed subsequently. Stools were persistently negative for occult blood. The temperature, white blood count, and sedimentation rate were elevated. Serial electrocardiograms confirmed the diagnosis of myocardial infarction (Fig. 1). Ten days after the thrombosis, auricular fibrillation developed, but the rhythm later reverted to normal. The blood pressure during the postinfarction period ranged from 100/60 to 120/70. The patient was discharged in good condition on the seventieth hospital day, six weeks after the infarction.

DISCUSSION

It appears that massive transfusions were a lifesaving measure in this patient. The absence of congestive heart failure during the postinfarction period is quite noteworthy since only four weeks previously cardiac decompensation had been a prominent finding.

If the sudden collapse of this patient was the result of "acute forward heart failure," then the heart was already incapable of handling the circulatory load, and it would seem that the additional strain of 2,200 c.c. of blood and plasma intravenously should have hastened a fatal outcome. That, instead, he made a rapid and uneventful recovery would support the view that the failure was peripheral in nature and that restoration of the effective blood volume was the significant factor in his survival. The foregoing facts suggest that in cases of myocardial infarction and shock without heart failure, it may be advantageous to treat this critical complication actively. It must be anticipated that cardiac decompensation will develop in some patients following such therapy, but it should be emphasized that this occurs in many cases without such treatment. If the peripheral circulatory collapse is not corrected, it appears probable that many patients will succumb immediately. With intravenous blood and plasma there may well be an appreciable number who will recover.

Immediate venesection after return of blood pressure from shock levels may be indicated in instances where congestive heart failure follows upon the increase in blood volume and the return of pooled blood to the effective circulation. The use of digitalis, diuretics, fluid restriction, and other measures should further aid the recovery of such patients, who might otherwise die in the acute shock phase.

SUMMARY AND CONCLUSIONS

A patient with profound peripheral vascular collapse accompanying myocardial infarction received 2,200 c.c. of blood and plasma within a period of forty minutes. Recovery was rapid and uneventful. Signs or symptoms of congestive heart failure did not develop.

It is suggested that serious consideration be given to the use of blood and plasma in the treatment of shock accompanying myocardial infarction.

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A RELATION BETWEEN THE SIZE OF THE HEART AND THE VELOCITY OF THE BLOOD

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DETERMINATION of blood velocity is a simple, inexpensive procedure which enjoys wide clinical popularity. David and Bouvrain,¹ in 1940, first reported on the relation of blood velocity to heart size, although Nylin reports he had begun work along this line in 1933.² Nylin and Malmström made their first report on this topic in 1941.³ One of us⁴ followed David and Bouvrain's suggestion and developed a relation between the size of the heart and the circulation time. We had not had access to Nylin's earlier publication at that time. The present report amplifies and modifies our previous finding.

METHODS

Patients were selected who were known to have heart disease. Many had been or were in various stages of congestive heart failure. Blood velocity was determined with Decholin† by the method of Winternitz, Deutsch, and Brüll.⁵ Each determination was made in duplicate. After an initial rest period in the supine position of fifteen minutes or more, 5.0 ml. of a 20 per cent solution of sodium dehydrocholate was injected into the antecubital vein. Three to five minutes elapsed between the first and second injection of the material. Other investigators have shown that there is little, if any, significant difference between the blood velocity determined thus and the velocity in patients who are in the basal state.⁶ Most of the determinations checked within a few seconds, although on one or two occasions gross discrepancies were noted which we interpreted as mistakes on the part of the patients. These errors were not included in the tabulations. A few patients experienced disagreeable reactions, none of which were of a serious nature. No cases other than the errors noted were excluded from the tabulations. In general, checks between the first and the second estimate were less good in patients with auricular fibrillation than in patients with a normal sinus rhythm.

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†Decholin was supplied through the courtesy of Mr. Paul de Haen of the firm of Riedel-de Haen, Inc., 105 Hudson St., New York City.

TABLE I. BLOOD VELOCITY FROM ARM TO TONGUE, RATIO OF TRANSVERSE DIAMETER OF THE HEART TO THE INTERNAL DIAMETER OF THE CHEST, AND THE CUBE OF THE RATIO OF THE TRANSVERSE DIAMETER OF THE HEART TO THE INTERNAL DIAMETER OF THE CHEST IN FORTY-ONE PATIENTS WITH KNOWN HEART DISEASE

CASE	CIRCULATION TIME (SEC.)	TRANSVERSE DIAMETER OF HEART/ INTERNAL DIAMETER OF CHEST	(TRANSVERSE DIAMETER OF HEART/ INTERNAL DIAMETER OF CHEST) ³
34	12.5	.615	.233
19	13.0	.572	.187
15	13.5	.564	.179
29	13.5	.574	.189
32	13.7	.595	.211
24	14.0	.540	.157
25	14.5	.545	.162
22	15.0	.494	.120
31	16.0	.588	.203
39	16.5	.656	.282
27	16.5	.568	.183
12	17.0	.647	.271
37	18.5	.634	.255
38	18.5	.637	.258
26	19.0	.563	.178
9	20.0	.604	.220
14	20.0	.604	.220
23	20.3	.526	.146
11	21.0	.673	.305
8	23.0	.518	.139
35	23.2	.625	.244
28	23.5	.568	.183
30	24.5	.584	.199
7	25.0	.560	.176
4	26.0	.643	.266
41	26.5	.711	.359
36	26.7	.633	.254
13	27.5	.655	.281
5	29.0	.632	.252
10	29.0	.630	.250
1	30.0	.629	.249
40	30.0	.710	.358
17	32.0	.750	.422
16	34.3	.696	.337
33	34.5	.602	.218
6	35.0	.600	.216
20	36.8	.692	.331
21	40.0	.750	.422
2	43.0	.723	.378
18	57.0	.744	.412
3	66.5	.796	.505
Mean	25.268	.626	.254
Standard deviation	±11.47	±.065	±.078

was first expressed as arm-to-tongue time in seconds. When these two data for each case were plotted with rectilinear coordinates, two things were immediately apparent. First, there was significant correlation and, second, a linear plot was only a first approximation. Several functions were tried, but the most linear relationship was between the logarithm of the circulation time and the TD/ID.

Teleroentgenograms were obtained in the routine manner near the time of the determination of blood velocity. The transverse diameter of the heart was taken as the sum of the distances from the midline to the outermost border of the heart to the right and to the left. The internal diameter of the chest was measured at the level of the fourth costochondral junction rather than the customary measurement lower in the rib skirt.

RESULTS

Forty-one cases are reported. The findings are summarized in Table I. The formulation of the relationship between heart size and blood velocity reported earlier by one of us¹ is found in this larger number of cases still to be statistically highly significant (Fig. 1). Heart size was expressed as the ratio of

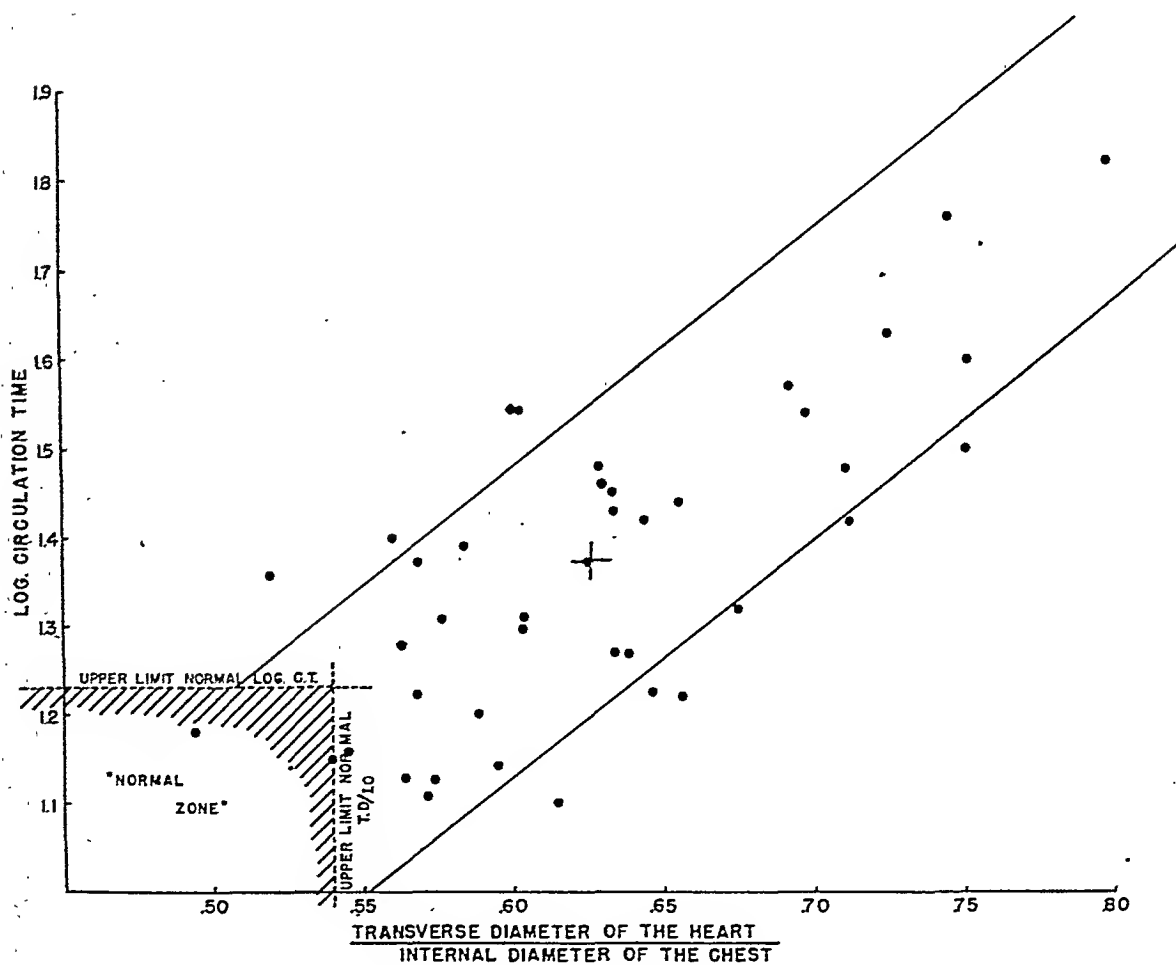


Fig. 1.—Relation of heart size $\left(\frac{\text{Total diameter}}{\text{Intrathoracic diameter}} \right)$ and log. circulation time.

the transverse diameter of the heart to the internal diameter of the chest (TD/ID). This ratio was utilized rather than absolute heart size because it tends to reduce to a common denominator variation due to stature and habitus. Blood velocity

TABLE I. BLOOD VELOCITY FROM ARM TO TONGUE, RATIO OF TRANSVERSE DIAMETER OF THE HEART TO THE INTERNAL DIAMETER OF THE CHEST, AND THE CUBE OF THE RATIO OF THE TRANSVERSE DIAMETER OF THE HEART TO THE INTERNAL DIAMETER OF THE CHEST IN FORTY-ONE PATIENTS WITH KNOWN HEART DISEASE

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was first expressed as arm-to-tongue time in seconds. When these two data for each case were plotted with rectilinear coordinates, two things were immediately apparent. First, there was significant correlation and, second, a linear plot was only a first approximation. Several functions were tried, but the most linear relationship was between the logarithm of the circulation time and the TD/ID

ratio. It was evident then, as it is now, that this empirical formulation has no physiologic rationale. It was offered as an observation without an explanation. ". . . . a correlation means nothing except statistical association between the variables, no matter how glamorous or seductive the suggestion as to casual relation may be."⁷

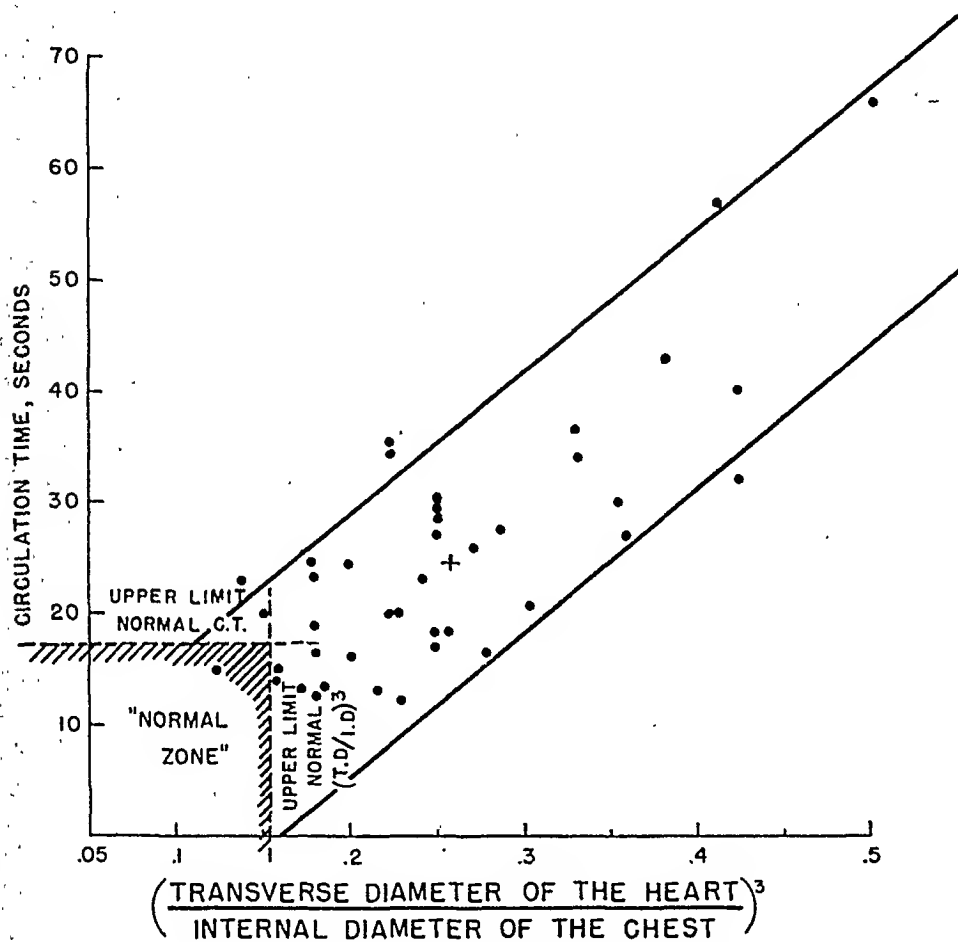


Fig. 2.—Relation of heart volume $\left(\frac{\text{Total diameter}}{\text{Intrathoracic diameter}} \right)^3$ and circulation time.

The larger volume of data here reported made it possible to examine other associative relationships more critically, and we have found one such relationship which probably has real physiologic significance. The TD/ID ratio is a linear measure of the heart. The cube of this ratio is a measure of heart volume. When this volume function is plotted against observed circulation time, a highly significant correlation is found (Fig. 2). The coefficient of correlation is +0.86 with a standard error of ± 0.16 . Parallel lines are drawn at plus and minus one standard deviation about the axis of the respective means. These include about 88 per cent of the cases. Seventeen seconds was taken as the "upper limit of normal" for circulation time and 0.54 as the "upper limit of normal" for the TD/ID ratio measured in the manner described. Therefore, the upper limit of normal for $(\text{TD}/\text{ID})^3$ is 0.15.

DISCUSSION

It is obvious that some relation might exist between the transverse diameter of the heart and the velocity of blood flow. In general, patients who have severe heart disease have enlarged hearts and the same group tend to have prolonged circulation times. Yet, scrutiny of similar patients with respect to certain other measurements, for example, elevated blood volume and elevated venous pressure, has not revealed any simple relation. It is generally true that a group of patients with high venous pressure will also, as a group, have high blood volumes,⁸ but a direct simple correlation does not exist within a group of patients in heart failure.⁴ This latter finding has been confirmed and some of the reasons for the lack of such a simple relation clarified.⁹ It is, therefore, interesting that relations of heart size to blood velocity can be shown to exist.

We chose the transverse diameter of the heart and the internal diameter of the chest as more readily available than such measures as frontal area or height-weight formulas. We agree with others¹⁰ that measurements of frontal cardiac areas in the teleroentgenogram are not reliable because the examiner has to draw most of the perimeter of the area he will measure. The transverse diameter of the heart is certainly one of the simplest and most reliable measures in common use,¹⁰ but one needs to be critical in employing it to avoid misleading silhouettes.¹¹

Selection of the level of the fourth costochondral junction for measurement of the internal diameter was based upon a suggestion to one of us some years ago by Dr. George Ramsey which, so far as we are aware, has not been published. Experience on our part has served to confirm his recommendation. At this level the chest is less subject to irrelevant variation than lower in the rib skirt. The value of securing the information desired from the film alone rather than from weighing and measuring the patient in addition is apparent. In our experience 0.54 is the upper limit of normal for the ratio between the transverse diameter of the heart and the internal diameter of the chest measured in this way.

Experiences to be published elsewhere have convinced us that, of the common methods of evaluating the circulation in cardiac impairment, the blood velocity is one of the least labile measures. It reflects the actual condition of the circulation much better, for example, than the venous pressure which is well known to fluctuate through any given day. On the other hand, the heart is only one of the numerous factors affecting the velocity of the blood. The peripheral circulation is certainly equally important, as is most strikingly seen in hyperthyroidism with heart failure. It is not the aim of this paper to advocate the determination of the velocity of the blood as more than one part of the study of impaired circulation but rather to demonstrate the simple relation which exists here within such a group of patients. This suggests that further exploration of the relation should give valuable new information about the circulation in impairment.

Over the past few years, Nylin has developed his concept of blood velocity as a function of the residual volume of the heart. At the time of the earlier work by one of us mentioned previously,⁴ we had not had access to Nylin's formulation. He had stated, "There appears to be a definite correlation between the

circulation time and the size of the heart in compensated cases of cardiovascular disease."³ More recently he has further explored this relationship^{2,12} and concluded that, "The prolongation of the circulation time . . . is not only an expression of the degree of stasis but also of the dilatation of the heart and thus of the residual blood in the heart."

In cardiac patients there is little doubt that Nylin's observations on the prolongation of the *duration* of the taste sensation² and the flattening of the arterial red cell dilution curve¹² are due in part to the increased amount of blood that injected material must mix with, in the heart among other places. Yet, there appears little reason to suppose residual blood in the heart could of itself slow the circulation and *substantially* delay the arrival of the *first portion* of the material at the sensitive organ by this mixing effect. The fundamental defect in congestive heart failure in all its stages is impaired *myocardial* function. The "law of the heart"¹³ is no longer obeyed and work is disproportionate to heart volume.^{14,15} "Residual blood in the heart" is only a secondary effect of cardiac dilatation, while cardiac dilatation is a primary effect of impaired myocardial function. It appears more logical to relate slowing of the circulation to the latter than to the former. The findings embodied in this report are in accord with Nylin's earlier formulation quoted in the foregoing.³ We are not inclined to accept a casual relation between prolongation of the circulation time and "residual blood in the heart" per se.

Since all these patients had known heart disease, a point of practical clinical interest is that eleven patients (27 per cent) were within "normal limits" of circulation time, while only three (7 per cent) were within "normal limits" of the TD/ID ratio. This suggests the roentgenographic measurement detects cardiac abnormality with greater accuracy than the blood velocity determination. Further, only one of the group (2.5 per cent) had both a normal TD/ID ratio and a normal blood velocity which suggests that both data together form an even better clinical criterion of cardiac abnormality.

SUMMARY

1. The correlation between heart size and circulation time reported earlier by one of us⁴ is confirmed as a statistical association, but it lacks an adequate rationale.
2. A highly significant correlation between a measure of heart volume and the arm-to-tongue circulation time in forty-one patients with known heart disease is described. This relationship is understandable in the light of current concepts of myocardial failure.
3. It is concluded that circulation time is proportional to relative heart volume in patients with heart disease, confirming the earlier formulation of Nylin.³

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ORIGIN OF LEFT CORONARY ARTERY FROM PULMONARY ARTERY

REVIEW OF THE LITERATURE AND REPORT OF TWO CASES

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THE origin of the left coronary artery from the pulmonary artery has intrigued clinicians and pathologists since the anomaly was first described in 1911.¹ A total of twenty-five cases, eighteen infants and seven adults, has been reported in which this was the only cardiac abnormality.

This lesion is rare, having been found in only one out of 6,800 consecutive autopsies at the Massachusetts General Hospital.² The two cases described herewith were encountered in the course of 7,800 consecutive autopsies at the Mount Sinai Hospital.

These cases have stimulated continuing interest because they furnish an opportunity to study changes in the heart when the left coronary artery is perfused in vivo with partially oxygenated blood at reduced pressure.

CASE REPORTS

CASE 1.—A 3-month-old white male infant was admitted to the Mount Sinai Hospital with a history of nonproductive cough and wheezing for one week. Pregnancy and delivery had been normal, and the infant weighed 8 pounds at birth. Weight gain had been satisfactory. One week before admission he developed a dry cough and fever. Examination at the pediatric clinic was negative except for some wheezing. Four days before admission, he was found to be improved. The night before admission the infant became feverish and dyspneic and coughed frequently.

Physical examination revealed a thin, pale, cyanotic, extremely dyspneic infant, with an anxious expression, who was perspiring profusely. Temperature was 102.8° Fahrenheit. Respirations were 100 per minute. The trachea was shifted slightly to the left and the left chest was somewhat retracted. There was flatness and bronchial breathing over the left upper lobe area; râles were heard at the left base, and occasional wheezes were heard throughout both lungs. The heart sounds were of fair quality, the heart rate was 200 per minute with regular rhythm, and there was a short blowing systolic murmur at the apex. The liver edge was felt two fingerbreadths below the costal margin.

X-ray examination on admission (Fig. 1) revealed enlargement of the heart to the left and a dense homogenous shadow in the left lower lung field. White blood cells were 7,900 per cubic millimeter.

On admission, the infant was considered to have pneumonia superimposed on congestive heart failure due to congenital heart disease. He was placed in an oxygen cubicle and given 3,000 units of penicillin every three hours and 0.25 Gm. sulfadiazine every four hours. He was

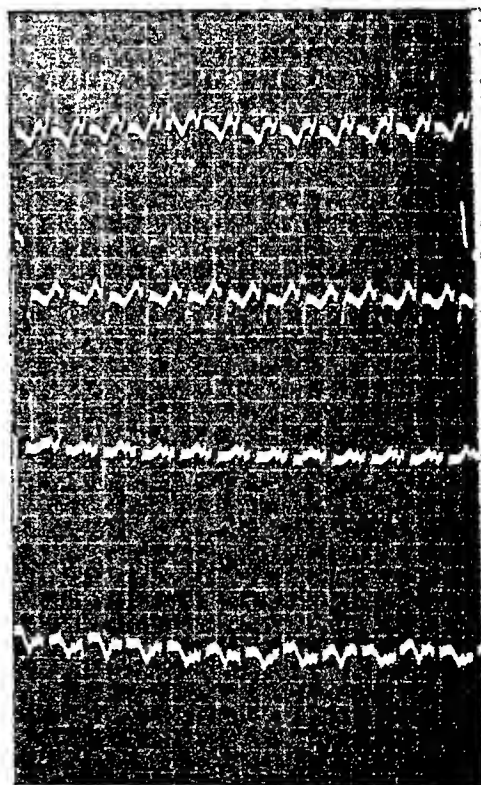
From the Laboratories, Division of Pathology, the Mount Sinai Hospital.
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Fig. 1.—Case 1. X-ray of chest taken on admission. Enlargement of heart to left, with accentuation of pulmonary vascular markings.



A.



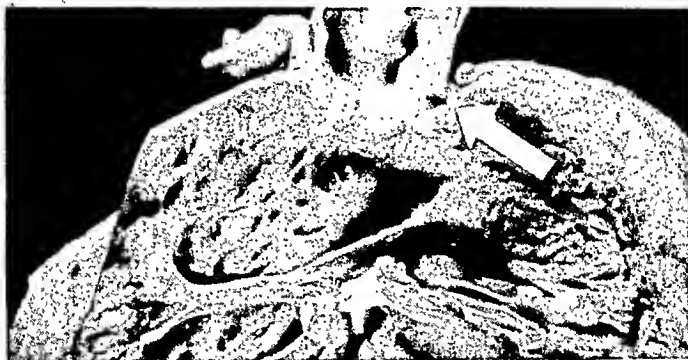
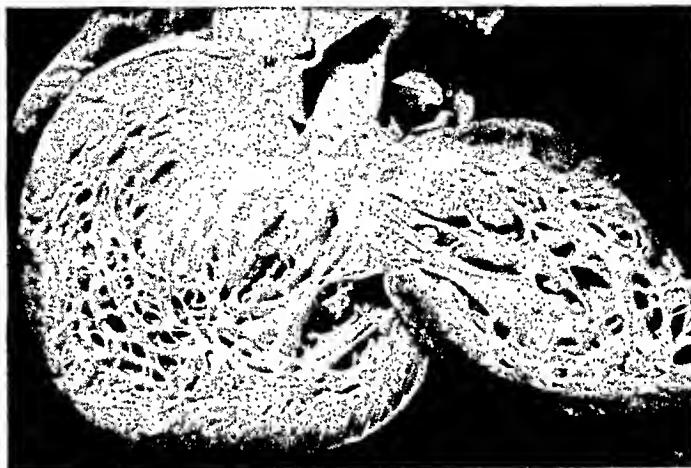
B.

Fig. 2.—Case 2. A, X-ray of chest taken on admission. Enlargement of heart to left, with accentuation of pulmonary vascular markings. B, Electrocardiogram taken on admission. No digitalis had been administered. Rate, 180. Tendency to left axis deviation. Slight depression of RST₁ and RST₂; inverted T₁ and T₂; biphasic T₄.

rapidly digitalized. The temperature gradually rose, and twelve hours after admission it had reached 105.8° Fahrenheit. There was no improvement in the dyspnea, and the infant died thirteen hours after admission.

Autopsy.—Autopsy* was performed eight hours after death. The findings were as follows: The heart weighed 102 grams (average normal, 27 grams). There was no free pericardial fluid

B.



A.

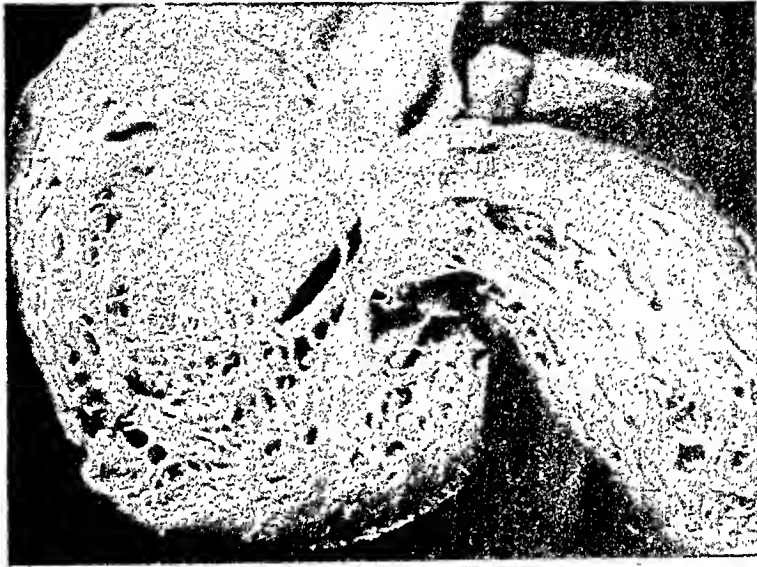
Fig. 3.—Case 1. A, Right ventricle. Arrow points to ostium of left coronary artery in left sinus of Valsalva of pulmonary artery. B, Left ventricle. Hypertrophy and dilatation, endocardial fibrosis, atrophy of anterior papillary muscle. Note absence of vascular opening in left sinus of Valsalva of aorta.

and the pericardial surfaces were smooth and glistening. There was a bluish discoloration over the epicardial surface of the left ventricle due to a very fine vascular network over an area 2 cm. in diameter. The heart was markedly enlarged. It was globular in shape because of bulging and rounding of the left ventricle and measured 7 cm. in its greatest diameter. The right auricle and tricuspid valve were normal; the latter measured 5 cm. in circumference. The right ventricle was slightly dilated and hypertrophied and measured 3 mm. in average thickness. Section of the right ventricle revealed normal-appearing myocardium. The pulmonic valve was normal; it measured 3.2 cm. in circumference. Just above the free edge was a vascular opening in the left sinus of Valsalva, which was the ostium of the left coronary artery (Fig. 3, A). This artery

*By Dr. L. Strauss.

branched soon after its origin and had a normal course and distribution; the vessel wall appeared normal. The pulmonary artery itself was not remarkable, and the ductus arteriosus was closed. The left atrium was slightly dilated and hypertrophied and the endocardium moderately thickened and gray. The mitral valve was normal; its circumference was 4.8 centimeters. The left ventricle (Fig. 3, *B*) was markedly dilated and bulged in a thinned area near the apex. The trabeculae were flattened, and the endocardium was extremely thickened, gray, and lusterless. The anterior papillary muscle was markedly atrophied and appeared as a gray fibrous band;

B.



A.

Fig. 4.—Case 2. *A*, Right ventricle. Arrow points to ostium of left coronary artery just above left sinus of Valsalva of pulmonary artery. *B*, Left ventricle. Hypertrophy and dilatation, endocardial fibrosis, atrophy of anterior papillary muscle. Note absence of vascular opening in left sinus of Valsalva of aorta.

in the thickened endocardium small white flecks could be seen. The myocardium of the left ventricle was 10 mm. in thickness near the base and became progressively thinner toward the apex, where it measured 2 millimeters. On section, there were gray patches beneath the endocardial lining and almost complete fibrous transformation in the aneurysmal portion near the apex. The outer portion of the myocardium was grayish-red, with a considerable amount of white flecking. The aortic valve was 3.2 cm. in circumference, and the right sinus of Valsalva gave origin to the right coronary artery, which was normal in appearance, course, and distribution. The left sinus of Valsalva contained no ostium.



Fig. 5.—Case 1. Left ventricle, anterior wall. Extensive fibrous replacement of myocardium.
Low power.



Fig. 6.—Case 1. Left ventricle, anterior wall. Dilated endothelial-lined myocardial sinuses.
Medium power.

Microscopic Findings.—

Left Ventricle, Anterior Wall, Near Apex: The endocardium was greatly thickened, being composed of fibrous connective tissue and elastic fibers. The myocardium was thickened and largely replaced by vascularized fibrous connective tissue, especially near the endocardial surface (Fig. 5). Many muscle fibers showed loss of striation and nuclei. The fibrous septa were abnormally thickened. Some cells contained vacuoles, which did not take glycogen stain. There was occasional calcium deposition in the muscle and also hyaline and fatty changes. No cellular reaction was noted. There were numerous endothelial-lined sinuses (Fig. 6) scattered through the myocardium, chiefly near the endocardial surface, some of which contained blood. An occasional sinus appeared to open into the ventricular chamber. In the walls of the smaller arterics there was marked thickening of the intima, with proliferation of muscle and elastic fibers, and splitting of the internal elastic lamella. The intimal muscle fibers were oriented longitudinally and radially with respect to the lumen of the vessel. The media was very thin, being at most three or four fibers in width. The adventitia was thickened, with proliferation of fibrous connective tissue both within and outside this layer.

Anterior Interventricular Septum: The septum was thickened, with hypertrophy of muscle fibers. There were occasional foci of fibrosis and exaggeration of the connective tissue septa. Vascular changes were found similar to those described in the anterior wall of the left ventricle (Fig. 7).

Left Anterior Papillary Muscle: There was almost complete fibrous transformation, and in areas beneath the endocardium some individual muscle fibers seemed to have been replaced by calcium (Fig. 8).

Left Atrium: There was moderate fibrous and elastic endocardial thickening, with slight hypertrophy of the muscle fibers.

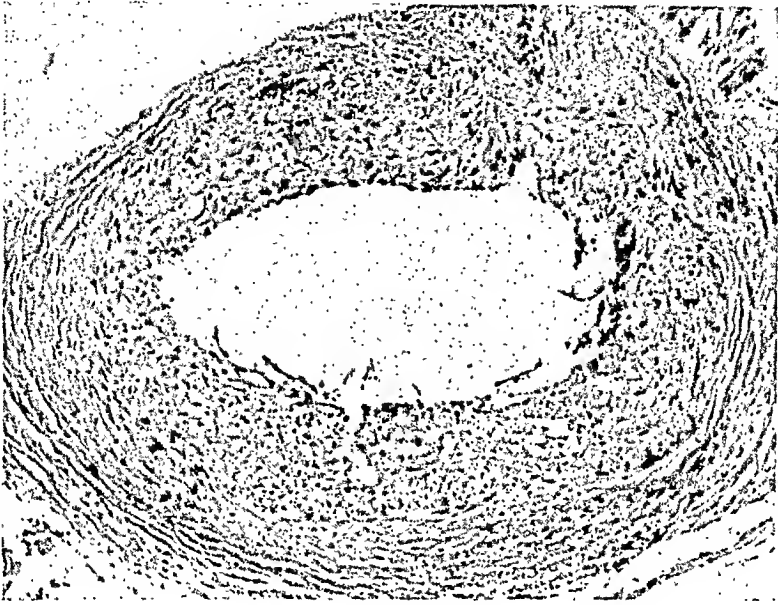
Left Posterior Papillary Muscle: Moderate fibroelastosis of the endocardium was present. There was slight fibrous replacement in the myocardial layer. Vessels were normal except for minimal intimal thickening of the smaller arteries. Myocardial sinuses were dilated.

No abnormalities were revealed in sections through the circumflex and anterior descending branches of the left coronary artery, the posterior descending branch of the right coronary artery, and several portions of the right ventricle and right auricle.

Diagnosis: (1) Origin of left coronary artery from pulmonary artery: dilatation and hypertrophy of left ventricle; myocardial fibrosis of left ventricle, with focal calcification, dilatation of myocardial sinuses, and musculoelastic intimal proliferation; atrophy of left anterior papillary muscle; diffuse fibroelastic thickening of endocardium of left ventricle; (2) bilateral bronchopneumonia; (3) atelectasis of left lung; (4) congestion and edema of liver; (5) hydrocele, left; (6) enlargement of thymus (37 grams).

CASE 2.—A 3-month-old female infant was admitted to the Mount Sinai Hospital with a history of grunting respiration since birth. Birth weight had been 7 pounds, 7 ounces. Pregnancy and delivery had been normal. At birth, several cutaneous hemangiomas were noted, which subsequently increased in size. Respirations had always been grunting in character, and there was transient cyanosis during crying. These symptoms increased in severity during the three days prior to admission.

Physical examination revealed a well-developed and nourished infant, who was pale, dyspneic, and cyanotic. The respirations were 70 per minute and grunting in quality. The alae nasi dilated on inspiration. The temperature was 99.6° Fahrenheit. Cutaneous hemangiomas were present over various parts of the body. The throat was congested and there were diminished breath sounds and dullness over the right lower lobe area. The heart was enlarged to the left on percussion, and sounds were of good quality with a rate of 180 per minute. No thrills or murmurs were heard. The liver edge was felt two fingerbreadths below the costal margin, and the spleen tip could be felt at the costal margin.



A.



B.

Fig. 7.—Case 1. Anterior interventricular septum. A. Small artery. Marked intimal thickening with thinning of media. Hematoxylin and eosin stain, medium power. B, Small artery, with thickened intima and fibrous thickening of adventitia. Weigert's elastic tissue stain and Van Gieson. Medium power. C, Same artery as shown in B. Phosphotungstic acid-hematoxylin stain. Medium power.



C.

Fig. 7.—*For complete legend, see opposite page.*



Fig. 8.—Case 1. Left anterior papillary muscle. Calcification of muscle fibers. Kóssa stain. Medium power.

On admission, hemoglobin was 76 per cent (12.9 Gm.). White blood cells were 17,600 per cubic millimeter, with 49 per cent segmented and 4 per cent nonsegmented polymorphonuclears, 44 per cent lymphocytes, and 3 per cent monocytes. The urine was acid, contained a trace of albumin, and there were 30 white blood cells per high-power field in the sediment. X-ray examination of the chest on admission (Fig. 2, A) revealed the heart to be considerably enlarged to the left, with prominence of vessel markings in both lungs. Electrocardiogram on admission (Fig. 2, B) indicated sinus tachycardia (rate 180), tendency to left axis deviation, moderately high voltage in Leads II and III, slightly depressed RS-T₁ and RS-T₂, inverted T₁ and T₂ and biphasic T₄.

The patient was placed in an oxygen cubicle, given 10,000 units of penicillin every three hours, and was rapidly digitalized. On this regimen, the symptoms of congestive heart failure disappeared within three days. Six weeks after admission, an attack of dyspnea, tachycardia, and acute enlargement of the liver occurred and responded well to digitalization. Because of the presence of many cutaneous hemangiomas, it was thought that a similar condition within the heart might account for the cardiac symptoms, and for this reason 1,200 roentgen units were administered over the left chest. Serial electrocardiograms revealed a bifid P₁; the RS-T segments in Leads I and II became less depressed, and T₂ became upright. During the ninth week of hospitalization, dullness on percussion of the entire left chest was noted, and an x-ray film was thought to reveal pleural effusion. On aspiration of the left chest, a small amount of blood-tinged, straw-colored fluid was withdrawn, which was sterile on culture. In the thirteenth week of hospitalization, there was rise in temperature to 104.2° F., which was accompanied by dyspnea and tachypnea. Despite therapy directed to combat congestive heart failure and infection, the patient rapidly failed and died after three months of hospitalization and at the age of six months.

Autopsy.—Autopsy* was performed fifteen hours after death. Findings were as follows: The heart weighed 100 grams (average normal, 34 grams). The pericardial sac contained a few cubic centimeters of clear straw-colored fluid, and the epicardial surface was smooth and glistening. The heart was strikingly enlarged, with the left border prominent and bulging. On the anterior wall of the left ventricle was an extensive, delicate vascular network which imparted a blue color to this area. Prominent vascular channels were noted also over the anterior surface of the pulmonary artery. The right auricle was slightly dilated. The foramen ovale was closed. The tricuspid valve was 5 mm. in circumference, and the leaflets were delicate and transparent. The right ventricle was slightly dilated and hypertrophied; its wall measured up to 5 mm. in thickness. The trabeculae carneae were prominent, and the endocardium was thin and transparent. The myocardium of the right ventricle appeared normal on section. The pulmonary valve was normally formed and measured 3 cm. in circumference. Four millimeters above the left sinus of Valsalva of the pulmonary artery was the widely patent ostium of the left coronary artery (Fig. 4, A). Just distal to the orifice, this artery branched in the usual fashion and had a normal course and distribution. The vessel was normal in width, the lumen patent, and the intima delicate and smooth. The ductus arteriosus was obliterated. The left atrium was normal except for slight endocardial thickening. The mitral valve was normally formed; the ring measured 5 cm. in circumference. The left ventricle (Fig. 4, B) was greatly dilated and hypertrophied and was converted into a wide aneurysmal sac with a bulging anterior wall and apex. At its base the posterior wall measured 10 mm. in thickness. Toward the anterior wall and the apex the wall became progressively thinner and measured only 1 to 2 mm. in the thin bulging area which was beneath the delicate vascular network observed on the epicardial surface. At its thinnest portion, the wall was transformed into fibrous tissue. The endocardium of the left ventricle was grayish-white, thickened, and lusterless, and beneath it were seen a few small flat yellow patches. The trabeculae carneae were thickened and prominent. The anterior papillary muscle was flat and white, and there were many white flecks in the surface. The posterior papillary muscle was only slightly flattened. The interventricular septum bulged toward the right. The aortic valve was normally formed; the ring measured 3 cm. in circumference. The right coronary ostium

*By Dr. L. Strauss.

was encountered in its usual position just above the right sinus of Valsalva of the aorta. The right coronary artery was normal in size, course, and distribution. There was no vascular opening in the left sinus of Valsalva.

Microscopic Findings.—

Left Ventricle, Anterior Wall: There was marked thickening of the endocardium which consisted principally of fibrous and elastic tissue. Chiefly near the endocardial surface were extensive areas of fibrous replacement of myocardium. Many muscle fibers showed loss of nuclei and striations. Capillaries and endothelial-lined sinuses were numerous; some of the latter appeared to enter the ventricular chamber. No cellular reaction was seen. The small arteries appeared normal.

Interventricular Septum, Anterior: The endocardium was thickened and fibroelastic. Most arteries showed marked intimal thickening, composed of muscle and elastic fibers. In some portions, the vessels were almost occluded by this process. The internal elastic lamella was shredded. The inner portion of the intima was in the form of a meshwork which did not stain with Sudan III. The media was much thinned. The adventitia was thickened and composed of a loose fibrillar network. There was moderate increase in perivascular connective tissue.

Left Ventricle, Posterior Wall: The endocardium was moderately thickened, with elastic and connective tissue fibers. There was extensive scarring of the myocardium; some areas showed vacuolization and loss of nuclei and of striations of muscle fibers. Areas of calcification were present within the myocardium and trabeculae. Myocardial sinuses were dilated.

Left Anterior Papillary Muscle: There was marked atrophy and almost complete replacement by scar tissue which contained large numbers of elastic fibers. Many foci of calcification were present throughout. The endocardium was moderately thickened.

Left Posterior Papillary Muscle: The endocardium was thickened and fibroelastic. There was moderate diffuse fibrosis of the myocardium, particularly beneath the endocardium. The vessels were normal.

No abnormalities were revealed in sections through the circumflex and anterior descending branches of the left coronary artery, the posterior descending branch of the right coronary artery, and several locations in the right ventricle and both auricles.

Diagnosis: (1) Origin of left coronary artery from pulmonary artery: dilatation and hypertrophy of left ventricle; myocardial fibrosis, left ventricle, with focal calcification, dilatation of myocardial sinuses, and musculoelastic intimal proliferation; atrophy of left anterior papillary muscle; fibroelastic thickening of endocardium of left ventricle; (2) atelectasis and confluent bronchopneumonia of left lung; (3) congestion of liver; (4) multiple hemangiomas of skin; (5) follicular cysts of ovaries.

SUMMARY OF THE LITERATURE

A summary of similar cases reported in the literature in infants and adults is given in Tables I and II, respectively.

The publication of these cases has encouraged two authors to describe patients in whom this diagnosis was suggested during life without post-mortem confirmation. Brown^{25a} reports the case of a 2-year-old boy with exertional dyspnea, cardiac enlargement to the left, gallop rhythm, and electrocardiographic changes suggestive of myocardial anoxia. At last report,^{25b} the child was 13 years of age, and the clinical and electrocardiographic changes persisted. Diaz²⁶ case was a 42-year-old man who, since infancy, had had exertional precordial pain and cyanosis which was not relieved by vasodilator drugs. The heart was enlarged to the left and the electrocardiogram revealed left bundle branch block,

TABLE I. SUMMARY OF REPORTED CASES OF ORIGIN OF LEFT CORONARY ARTERY FROM PULMONARY ARTERY IN INFANTS

NO.	AUTHOR	AGE (MO.) SEX	CLINICAL COURSE	PATHOLOGIC FINDINGS	REMARKS
1	Abrikossoff ¹	5½ F	Not given	Hypertrophy and dilatation of left ventricle with aneurysmal dilatation; endarteritis of coronary vessels; calcific replacement of myocardium; flattened left anterior papillary muscle	Believes anomaly due to misplaced coronary artery anlage
2	Cazzaniga ³	4 F	Sudden death; always in good health previously	Hypertrophy and dilatation of left ventricle, with endocardial thickening; diffuse fibrosis of left ventricle and septum; perivascular cellular infiltration; no changes in vessels; left anterior papillary muscle atrophied and scarred	Believes that an abnormal formation of the septum primum unlikely in the etiology of this anomaly
3	Heitzmann ⁴	3½ F	Died in attack of syncope and cyanosis	Hypertrophy and dilatation of left ventricle, with aneurysmal dilatation; flattening of left anterior papillary muscle; calcification in anterior wall of left ventricle and anterior papillary muscle; myocardial necrosis and fibrosis; endocardial thickening	Likens these changes to those found in coronary sclerosis
4	Kiyokawa ⁵	4*	Attacks of cyanosis and convulsions	Heart greatly enlarged; left ventricle hypertrophied and dilated, with aneurysmal dilatation at apex; septum deviated to right; focal areas of fibrosis, necrosis, congestion, and round-cell infiltration; vessels normal	Hydropericardium; hydrothorax; congestion of lungs and liver
5	Krumbhaar ⁶	10 F	Not given	Heart weight, 136 grams (normal, 39); hypertrophy and dilatation of left ventricle; vacuolar degeneration and areas of fibrosis; marked fibrosis of left anterior papillary muscle and anterior portion of septum	Believes that coronary anomaly did not cause pathologic changes

6	Heidloff ⁷	7½ F	Dyspnea for 4 mo.; retarded development; sudden death	Heart weight, 127 grams (normal, 27); deposits of fibrin over epicardium of left ventricle; right heart slightly enlarged; left auricle thickened and dilated; left ventricle dilated but not hypertrophied; aneurysmal dilatation of left ventricle, with calcification; vessels normal	Believes enlargement of heart due to hypertrophy of right ventricle; left lung atelectatic
7	Abbott ⁸	3*	Hoarseness	Excessive dilatation and hypertrophy of left ventricle	
8	Scholte ⁹	2½ F	Bronchopneumonia	Dilatation and hypertrophy of left ventricle; fibrosis, fatty changes, focal areas of necrosis, and calcification in left ventricle; flattening of left anterior papillary muscle; thickening of endocardium	Likens these changes to those found in coronary occlusion
9	Bland, White, and Garland ²	3 M	Attacks of dyspnea, sweating and pallor for 2 wk., precipitated by nursing; x-ray, diffuse enlargement; ECG, low voltage, inverted T _{1,3,5}	Heart weight, 91 grams (normal, 25); dilatation and hypertrophy of left ventricle, with increased thickness due to increase in number of muscle fibers and fibrosis; subendocardial fibrosis; hydropic changes in some muscle cells	Likens lesions to those found in coronary sclerosis; ECG changes also similar; attacks of sweating and pallor, thought to have been anginal in nature
10	Sanes and Kenney ¹⁰	3 M	Vomiting for 3 wk.; difficulty in breathing for 3 days; x-ray, enlarged heart	Heart weight, 95 grams (normal, 25); dilatation and hypertrophy of left ventricle, with aneurysmal dilatation at apex; fibrosis in myocardium of left ventricle; calcification and marked fibrosis of left anterior papillary muscle; deviation of septum to right; areas of necrosis in myocardium of left ventricle	Hydropericardium; likens myocardial changes to those due to excess amount of lactic acid in blood
11	Bartsch and Smekal ¹¹	3 M	Not given	Dilatation and hypertrophy of left ventricle; aneurysmal dilatation at apex; deviation of septum to right; endocardium thickened, with round-cell infiltration; foci of fibrosis throughout, with localized calcification at apex and anterior wall of left ventricle	

*Sex not given.

TABLE I. SUMMARY OF REPORTED CASES OF ORIGIN OF LEFT CORONARY ARTERY FROM PULMONARY ARTERY IN INFANTS—CONT'D

NO.	AUTHOR	AGE (MO.) SEX	CLINICAL COURSE	PATHOLOGIC FINDINGS	REMARKS
12	Haferkorn ¹²	4 F	Wheezing and cough since age of 7 wk.; difficulty in breathing at 3½ mo.; attacks of dyspnea, with anxious facial expression; x-ray, enlargement of heart to left	Dilatation and hypertrophy of left ventricle, with some enlargement and hypertrophy of right ventricle	Compression atelectasis of left lower lobe; cites symptom complex, clinical findings, and believes this to be a clinical entity
13	Linck ¹³	8 F	Not given	Heart weight, 110 grams (normal, 37); hypertrophy and dilatation of left ventricle; areas of myocardial fibrosis, with hyaline changes in muscle fibers	
14	Chown and Schwalm ¹⁴	5 M	Attacks of pallor, cough, cyanosis, fever	Heart weight, 70 grams (normal, 29); veins and myocardial sinuses dilated; hypertrophy and dilatation of left ventricle, with thickening of endocardium; left anterior papillary muscle vestigial; degeneration in myocardium of both ventricles, with large amount of fibrous replacement in left ventricle	Hydropericardium; congestion of liver; believes anomaly due to defective placement of coronary artery anlage
15	Barnard ¹⁵	5 F	At age of 19 wk., unable to swallow and gain weight; bulge in left chest; x-ray, enlargement of heart	Hypertrophy and dilatation of left ventricle; endocardial thickening, especially over trabeculae carneae; patchy necrosis and fibrosis, particularly subendocardially; coronary vessels normal	Atelectasis of left lower lobe; congestion of spleen and liver; believes anoxic changes may have started in fetal life

16	Benešová ¹⁶	2½ F	Dyspnoic and cyanotic; x-ray, enlargement of heart to left; died suddenly	Balloonlike enlargement of left ventricle, with atrophied papillary muscles, thickened endocardium; aorta slightly narrower, than pulmonary artery; endocardial thickening, consisting of loose connective tissue and fibroblasts; necrosis, fatty infiltration found particularly in inner half of myocardium; no inflammatory reaction found; calcification in anterior wall	Injection of right coronary artery revealed collateral circulation with left; musculoclastic intimal proliferation in some arteries
17	Soloff ¹⁷	4½ M	Attacks of pain, cyanosis, dyspnea, precipitated by feeding	Heart weight, 120 grams (normal, 30); dilated veins beneath epicardium of left ventricle; normal coronary artery distribution; no intercommunication found; right coronary ostium smaller than normal, left coronary ostium wider; embryonic sinusoids present; acute hydropic, fatty, and necrotic changes in myocardium with fibrosis and calcification	Believes this represents a syndrome in infants, that the anomaly is due to misplacement of the coronary artery anlage, and that the thinness of the media of the left coronary artery is due to diminished intraluminal pressure
18	Proescher and Baumann ¹⁸	13 F	Fever, wheezing, cough, anorexia, vomiting; left chest splinted; sudden death	Heart weight, 180 grams (normal, 42); visceral pericardium thickened over anterior left ventricle; left ventricle dilated and hypertrophied, with deviation of septum to right; left coronary ostium narrower than normal; embryonal sinusoids present; muscle fibers atrophic, elongated, fragmented, with fibrous tissue replacement; remnants of degenerated, necrotic, calcified muscle fibers present; endocardium thickened; perivascular fibrosis and intimal thickening	Left pyothorax; atelectasis of left lower lobe; believes persistence of sinusoids indicates developmental failure; remarks that these cases occur in females twice as often as in males

Since the submission of this report, Eidlow and Mackenzie (Am. Heart J. 32: 243, 1946) described the case of a female infant, normal at birth, who, at the age of 3 months, began to have attacks of dyspnea, choking associated with feeding, and paroxysms of cyanosis, dyspnea, and tachycardia. On x-ray examination, the heart was enlarged to the left and right, and there was partial atelectasis of the right upper lobe. An electrocardiogram revealed inversion of T₁ and T₂. These clinical, x-ray, and electrocardiographic findings directed the authors to the diagnosis of anomalous origin of the left coronary artery. The infant died at the age of 4 ½ months with signs suggesting pneumonia. At autopsy the heart weighed 85.3 grams (normal, 27). The left coronary artery arose from the pulmonary artery. All heart chambers were dilated, and the left ventricle was markedly dilated and hypertrophied, with fibrosis of the inner third of the wall. There was atrophy and vacuolization of muscle fibers. No embryonic sinusoids were seen. The endocardium of the left ventricle was thickened and fibrotic. There was slight medial thickening of the smaller coronary artery branches but no other abnormalities of the vessels. Pneumonia of the left lung and atelectasis of the right upper lobe were present.

TABLE II. SUMMARY OF REPORTED CASES OF ORIGIN OF LEFT CORONARY ARTERY FROM PULMONARY ARTERY IN ADULTS

NO.	AUTHOR	(YR.) SEX AGE	CLINICAL COURSE	PATHOLOGIC FINDINGS	REMARKS
1	Abbott ⁸	64 F	Not given	Hypertrophy, fibrosis and fatty changes; right coronary artery expanded near origin into a thick-walled loop and tortuous and thick-walled throughout its course; left coronary artery thin-walled, apparently originating in a sinus from the pulmonary artery	
2	Kockel ¹⁹	38 M	Episodes of precordial pain for a few years; died suddenly	Hypertrophy and dilatation of left ventricle; right coronary artery widened; no communication demonstrable between the coronary arteries; two fibrotic patches near bundle of His	Believes right coronary artery had assumed some function of the left
3	Rübbardt ²⁰	27 M	Died suddenly while working with pneumatic drill	Hypertrophy and dilatation of left ventricle; fibrous replacement of muscle fibers; no acute inflammation or degeneration found; right coronary artery widened; left coronary artery does not supply as much of myocardium as normally	Believes the sudden death due to anoxemia, brought on by demand for more oxygen, with supply limited by the anastomotic connection between right and left coronary arteries
4	Dietrich ²¹	53 M	Sick as child; thought to have had valvular disease; hypertension and auricular fibrillation present; episodes of angina	Large areas of subendocardial calcification; dilatation and hypertrophy of both sides of heart; both coronary arteries tortuous and dilated but distribution normal; right coronary artery sclerotic only near origin; intimal thickening in left coronary artery found only in myocardial branches	Believes dilatation and tortuosity of coronary arteries to be manifestation of adaptation, allowing individual to survive

5	Orsós ²²	17 F	Sudden death after exertion	Heart weight, 390 grams; dilatation of both ventricles; myocardial fibrosis of left ventricle, with appearance that of infarction; normal course of coronary arteries	Believes increased demands at time of puberty precipitated terminal episode
6	Ruddock and Stehly ²³	30 M	Sudden death during exertion	Heart normal in size; right coronary artery dilated, supplying all portions of myocardium except in the area of the left anterior descending artery; anastomoses between arteries demonstrable; no myocardial changes seen	Believes dilatation of right coronary artery an adaptation of coronary circulation and that myocardial damage was prevented by anastomoses
7	Helpern ²⁴	32 M	Sudden death; no known history of heart disease; death possibly due to barbiturate poisoning	Heart weight, 450 grams; dilatation and hypertrophy of left ventricle, with thickened endocardium; patch of fibrosis at apex of left ventricle; right coronary ostium greatly enlarged; both coronary arteries dilated and tortuous throughout their courses; dilated sinusoids in myocardium; only anterior wall of left ventricle supplied by left coronary artery; no anastomoses found between coronary arteries; some arteries in left ventricle show musculoclastic intimal proliferation; slight dilatation and hypertrophy of right ventricle	

with increased P-R intervals and RS-T elevations on exercise. Both authors, while expressing confidence in their diagnosis, call attention to the difficulties in ruling out other possible causes for the clinical findings. The long history, starting in infancy, is not reminiscent of any of the autopsied cases reported in adults, and the electrocardiographic changes are not similar to those found in the second case reported here nor the case of Bland, White, and Garland.²

Two cases have been reported in which the right coronary artery arose from the pulmonary artery, while the left coronary artery arose from the aorta. The patients died at 30 and 61 years of age, respectively, from unrelated causes, and in neither instance was there evidence of myocardial disease. In both instances, the left and right coronary arteries were dilated. In the first patient,²⁷ anastomoses between the branches of the vessels were detected. The right coronary artery was thin-walled and appeared rather like a vein. In the other instance,²⁸ the left coronary artery was thought to assume some of the function of the right coronary, and collateralization of the left coronary artery was abundant.* It may be assumed that when the right coronary artery is supplied with blood directly from the pulmonary artery, sufficient oxygen is available to allow the myocardium supplied by the right coronary artery to function, and that collateralization results as an adaptation of the coronary circulation to this unusual condition.

Two cases have been reported in which both coronary arteries arose from the pulmonary artery: In Grayzel and Tennant's²⁹ case, other cardiac abnormalities were present, the infant lived only a few hours, and the heart was not enlarged. Limbourg's³⁰ case had no associated cardiac anomalies and lived for ten days. The heart was normal in size and the left ventricle was slightly enlarged, with fatty infiltration of the myocardium. Apparently, when both coronary arteries receive blood from the pulmonary artery, there are insufficient compensatory factors available to maintain life beyond a few days.

DISCUSSION

Introduction.—The average blood pressure within the right ventricle is normally approximately one-sixth of that in the left ventricle. Thus, in the cases here referred to, the blood pressure within the left coronary artery is considerably below normal. The normal average oxygen content of blood within the right ventricle is approximately 12 to 14 volumes per cent, while the oxygen content of arterial blood is approximately 19 volumes per cent. The normal arteriovenous difference of the greater circulation (between aorta and right ventricle) is therefore 5 to 7 volumes per cent. The normal arteriovenous difference of the coronary circulation (between aorta and coronary sinus) is 10 to 15 volumes per cent. Not only does cardiac muscle respond by ceasing to function normally

*Since the submission of this report, an unpublished third case has been furnished, through the courtesy of W. A. Bennett, from the records of the Mayo Clinic. The patient was a 74-year-old man who died in congestive heart failure. The heart weighed 550 grams, and there was an old infarct at the apex with focal fibrosis of the septum. The identity of the right coronary artery was established only by microscope examination, inasmuch as the gross appearance was that of either a vein or an artery. There was more marked sclerosis of the left coronary artery than of the right. No collateralization was mentioned.

when a slight oxygen debt is incurred, but also as the ventricle dilates and the muscle fibers are lengthened, more oxygen is required for the same amount of work.³¹ Therefore, in the cases reported here, it may be assumed that the heart was deprived of sufficient oxygen for normal function.

Judging from the relative infrequency with which symptoms are mentioned before the age of 2 months, it would seem that for the first weeks of life the blood perfusing the left coronary artery is sufficient to maintain some degree of integrity of the myocardium. However, the growth of the infant imposes increasing demands which cannot be met, and the heart begins to fail. It is also possible that the gradual obliteration of the ductus arteriosus, usually complete at about the third month,³² withholds an additional source of oxygen from the left coronary circulation. According to Wiggers,³³ the heart muscle will hypertrophy upon constant stretching of the muscle fibers, as occurs in heart failure, and also when the heart is required to work nearer its reserve limit (as when more work is demanded without a corresponding increase in oxygen supply); both of these situations obtain in the condition we are discussing. Moreover, as Wearn³⁴ has demonstrated, the hypertrophied heart suffers a relative reduction in its blood supply, for the vascularization per unit weight falls and metabolic exchange is hindered. Anoxia leads inexorably to the fatal termination. It therefore appears that the pathologic changes found at necropsy represent the end stage of severe chronic anoxia of that portion of the heart furnished blood by the left coronary artery.

Etiology.—The coronary arteries are first seen as outpouching endothelial buds in the wall of the aortic bulb. Later, the bulbar septum forms to separate the aorta from the pulmonary artery. Two theories have been presented to explain the cause of the anomalous origin of one or both coronary arteries from the pulmonary artery:¹ (1) that the coronary artery anlage arises in the wrong location in the wall of the aortic bulb, so that the normally forming septum includes the coronary artery within the pulmonary artery instead of the aorta and (2) that the coronary artery anlage is normally disposed, but the bulbar septum forms in the wrong plane and incorporates one or both coronary arteries within the pulmonary artery. Cases have been reported in which the anomalous origin of the left coronary or of both coronary arteries from the pulmonary artery was associated with other cardiac defects,³⁵ and these would seem to be examples of an abnormally forming septum, as in the second theory mentioned previously. However, in all the cases summarized in Tables I and II, no associated cardiac abnormalities were reported, so it is most probable that these instances were the result of an abnormal position of the coronary artery anlage. The greater incidence of anomalous origin of the left coronary artery, as compared with the right, may be explained by the proximity of the left sinus of Valsalva of the aorta to the septum of the truncus arteriosus, with the result that a small displacement of its anlage would cause the left coronary artery ostium to fall within the pulmonary artery. The corresponding right sinus of Valsalva is much further from the septum, so that a considerable displacement of the right coronary artery anlage would be required to cause the anomalous origin of this vessel from the pulmonary artery.

Sex Incidence.—Proescher and Baumann¹⁸ called attention to an apparent sex predilection of this anomaly. In the literature they cited, there were twice as many female as male subjects. Of the cases in this series where sex was mentioned, there were fourteen female and eleven male patients, including twelve female and six male infants and two female and five male adults.

Clinical Course.—It will be noted that several of these infants died suddenly, while others had repeated attacks of cyanosis and dyspnea, particularly associated with nursing. The latter symptoms prompted Bland, White, and Garland² to suggest that these were episodes of angina pectoris due to transient myocardial anoxia. Haferkorn¹² and, later, Soloff¹⁷ felt that when this syndrome was associated with x-ray evidence of cardiac enlargement to the left and consistent electrocardiographic findings, the diagnosis could be made during life. In the first case reported here, there was no history of these transient attacks, while in the second case there had been transient cyanosis during crying since birth.

In several cases, the left ventricle was found to compress the left lung so that there was atelectasis of the left lower lobe. In each of the cases reported here, the left lung was collapsed due to compression by the enlarged left ventricle. The atelectasis undoubtedly contributed to the anoxemia.

Of the seven adults, four died unexpectedly, and three of these had no reported previous illness or disability. It is not clear just how much the vascular anomaly contributed to the clinical findings in Dietrich's²¹ case. In Kockel's¹⁹ case, two fibrotic patches near the bundle of His may have had some significance. In the latter instance, the patient had periodic precordial pain for several years.

Electrocardiographic Changes.—Bland, White, and Garland² presented the only electrocardiogram in the literature in a case of this type. There was low voltage and T-wave inversion in all leads, without axis deviation. Case 2 of this report revealed high voltage in Leads II and III, RS-T and T-wave changes characteristic of myocardial anoxia, and a tendency toward left axis deviation.

Pathology.—

Introduction: Any interpretation of pathologic findings in infants is tempered by the many imponderable physiologic factors attending growth. No doubt the tissues of an infant will respond to a given stimulus in a different manner than the tissues of an adult. For instance, the hypertrophy associated with congenital valvular lesions may involve a fourfold increase in the size of an infant heart, a situation almost unknown in adults even with heart disease of many years' standing. While stimuli are acting upon them, the tissues have certain demands which vary from age to age, and thus, in these infants, the reaction of the myocardium to chronic anoxia will be different in form and in tempo.

Duration of the Pathologic Changes: Barnard¹⁵ believes that the pathologic changes described in these cases may have begun in fetal life. Quoting Barcroft's studies revealing that inferior and superior caval blood streams take separate pathways in the fetal circulation, he maintains that even before birth

there would be less oxygen provided to the left coronary than to the right coronary artery. However, the youngest patient in this series was $2\frac{1}{2}$ months old at death, and since the findings were compatible with a process of this duration, it is unnecessary to attribute a greater age to the pathologic process. Also, in Limbourg's³⁰ patient, who died at 10 days of age, both coronary arteries arose from the pulmonary artery, yet the heart showed minimal changes. It is therefore unlikely that damage in these cases developed prenatally.

Pathology and Age at Death: The age of these patients at death is a matter of great interest. Of the twenty-seven cases, twenty were $2\frac{1}{2}$ to 13 months old at death. The seven adults were 17 to 64 years of age at death. Why did the majority of these patients die in early infancy, and why did the remainder, having survived early infancy, live until at least early adult life?

It is obvious that, with unimportant variations, the morbid lesions found in the two cases presented here duplicate those reported in the eighteen other infants.

One is impressed that the hearts in the adult group had certain characteristics in common. The right coronary artery was enlarged in most cases so that in some it assumed a cirroid form. In all except two cases, the left coronary artery was also enlarged. Also, in four of the seven cases, the right coronary artery appeared to have taken over the greater part of the coronary circulation. Did these individuals survive to adult life because of congenital variations in the distribution of the coronary arteries, or are these variations a manifestation of adaptation which allowed these few individuals to survive their infant years? Acknowledging the rarity of such congenital variations on the one hand and the well-known development of collateral circulation in disease of the coronary arteries on the other, the latter alternative seems to be correct.

In three of the seven adults, there was no change reported in the myocardium or the endocardium, so that in all probability the collateralization of the coronary circulation must have begun in early infancy, before any irreversible changes had taken place.

Hypertrophy and Dilatation: Although there is no record of blood pressure in these cases, it is unreasonable to assume that hypertension entered into the pathogenesis of the myocardial lesions. The hearts were generally four times the normal weight, and dilatation and hypertrophy were confined for the greatest part to the left ventricle. Possible physiologic processes underlying the hypertrophy have been outlined in the foregoing. The increased weight of the hearts is ascribable to hypertrophy of muscle fibers and increase in fibrous connective tissue. Almost all the reported cases were described as being in congestive heart failure at some time.

The right ventricle was dilated in several instances. This can be attributed to the failure of the left ventricle and to the functional insufficiency of the left anterior papillary muscle. It is also possible that the marked bulging of the interventricular septum to the right, mentioned in several cases, aggravated the already existing strain on the right ventricle.

Localization of the Lesions: Among the twenty cases reported in infants, including the two present cases, there was a striking uniformity in the distribution of the lesions. The effects of long-standing anoxia were manifest in those portions of the heart supplied by the left coronary artery: the anterior portion of the interventricular septum and the anterior and lateral walls of the left ventricle.³⁶ The majority of authors mentioned shrinking, fibrosis, and calcification of the left anterior papillary muscle, which not only derives its blood supply solely from the left coronary artery, but, from the standpoint of the coronary vascular tree, is at the greatest distance from the ostium of the left coronary artery.³⁶ Where the right coronary artery could be expected to assume part of the burden, such as in the posterior wall of the left ventricle, the changes, while still present, were of lesser degree; in the right ventricle, supplied completely by the right coronary artery, there were no abnormal findings except for slight dilatation and hypertrophy.

Calcification: In twelve of the twenty-seven cases, calcification of the myocardium was described. This usually took the form of actual replacement of individual muscle fibers and was most marked in the left anterior papillary muscle. In the two cases reported here, calcification was most marked in the areas of the greatest scarring. We agree with Abrikossoff¹ and believe that calcification follows necrosis of muscle fibers.

Whereas calcification of the myocardium due to coronary artery disease is only occasionally found,³⁷ it is frequently found in lesions such as congenital atresia or stenosis of the aortic valve in children, within areas of scarred myocardium.³⁸ The myocardium in children appears more prone to calcify.³⁸ Perhaps this observation is connected with the finding that values for serum calcium, inorganic phosphorus, and phosphatase are significantly higher in children than in adults.³⁹

Endocardial Thickening: In all the cases reported in infants, there was marked thickening of the endocardium, composed of fibrous and elastic tissue. The localization of this process within the left ventricle and the coincident changes in the underlying myocardium leave little doubt as to the common etiology. Fibroelastic thickening of the endocardium, termed variously fetal endocarditis⁴⁰ and endocardial fibroelastosis,⁴¹ has been reported in infants with and without myocardial changes and with and without valvular disease. Several cases have been reported in association with congenital aortic atresia and stenosis,⁴² where both coronary arteries received all or most of their blood supply from the pulmonary artery through the ductus arteriosus. It would be anticipated that under these circumstances the left ventricle would suffer the most severe anoxia, since it is under greater work demands than the right ventricle. In the cases reviewed by Farber and Hubbard,⁴² the endocardial and myocardial changes were confined to the left ventricle and were very similar to those found in the cases presented here. The likelihood therefore exists that at least some of the cases reported as fetal endocarditis and endomyocarditis were indeed due to anoxic changes caused by perfusion of the coronary arteries with partly oxygenated blood at low pressure. Gross⁴⁰ believes that the endocardial thickening is primary and

serves to seal off the vascular channels between the chamber of the ventricle and the myocardium, thus causing stasis in the myocardial sinuses and anoxia of the myocardium. In the cases reported here, anoxia seems to be sufficient reason for the myocardial and endocardial changes.

Collateral Circulation: Lowe⁴³ has found that when occlusive disease alters the pressure gradient between branches of the same artery, redistribution of blood supply is encouraged, and new routes and anastomotic channels develop rapidly. By the same token, collateralization in these infants should be enhanced because of the low pressure within the left coronary artery and its branches associated with normal pressure within the right coronary artery. This stimulation would be apparent initially only in the peripheral portions of the area supplied by the left coronary artery and would continue as long as the pressure differential existed. Apparently, in the adults in whom the right coronary artery was found to supply almost all the heart musculature, this process of collateralization had reached the maximum potential, in that the pressure within the distal branches of the right coronary collaterals approached the pressure within the adjacent remaining branches of the left coronary artery. In the infants, such collateralization may not have been evident because of the rapid progressive course.

Myocardial Sinuses: Several authors^{14,17,18,24} have called attention to the presence of endothelial-lined, blood-filled spaces in the myocardium in these cases and have expressed the opinion that there is abnormal persistence of the embryonic sinusoids which provide circulation in the myocardium during early fetal life. In both the cases presented here, dilated myocardial sinuses were found in the wall of the left ventricle, but in no other location, and several of these spaces appeared to communicate with the ventricular cavity.

Wearn³⁴ has shown that in addition to the Thebesian vessels, there are other communications between the lumen of the heart and the vessels within the wall. Under ordinary circumstances, there is little blood flow in these vessels because of the approximate equality of pressures within the chamber of the ventricle and the mural vessels. However, in this situation, where the pressure within the left ventricle is much higher than that within the myocardial vessels of the left ventricle, it is reasonable that there should be flow of blood through the Thebesian as well as the arterioluminal and sinusoido-luminal vessels and therefore possible that the myocardial sinuses seen histologically in these cases represent functioning communications.

Changes in Arteries: In both of the cases reported in this paper, in the smaller arteries in the wall of the left ventricle and the interventricular septum there was found intimal hyperplasia consisting of proliferation of muscle and elastic fibers, the former being oriented radially and longitudinally with respect to the vessel wall. In places, the lumen was almost occluded by the intimal proliferation. The internal elastic lamella was shredded. The media was thin, being reduced to the thickness of three or four fibers at some places. It is possible that the medial thinning may have been due in part to the intimal

thickening itself, the media being compressed by the growing intima. There was increase in fibrous connective tissue in the adventitia and perivascular zone. The larger arteries appeared normal. In the posterior wall of the left ventricle, minimal intimal thickening was present. No remarkable vascular changes were seen in the right ventricle.

These findings are similar to those illustrated by Abrikossoff,¹ who described the process as productive endarteritis and considered it to be secondary to the myocardial changes. Benesová¹⁶ described vascular changes in her case which were similar in type and distribution to those we have described. Dietrich's²¹ case was an adult and showed severe arteriosclerosis of the larger branches of the right coronary artery, while the smaller branches were normal. On the other hand, while the larger branches of the left coronary artery were normal in appearance (except for dilatation), the myocardial branches exhibited the same changes that were found in the cases reported here. Helpern's²⁴ case showed similar changes in the myocardial branches of the left coronary artery.

Soloff¹⁷ described dilatation of the left coronary artery, with thinning of the media, and considered this a response to diminished intraluminal pressure. He did not mention intimal changes.

Zinck,⁴⁴ describing normal vessels in infant hearts, mentioned musculo-elastic intimal thickening and hypertrophied media and adventitia at divisions of the main coronary arteries and also the myocardial branches. He considers these to be throttle arteries, with the function of regulating the blood flow through the end arteries of the heart. The medial hypertrophy he describes is in sharp contrast to the thinning found in the cases reported here. Arteries with these features are certainly rare in adult and infant hearts. I have examined routine sections of twenty-four infant hearts removed at consecutive autopsies, including twelve without heart disease and twelve with congenital heart disease, and have not found the features described by Zinck. The likelihood remains, therefore, that the intimal thickening seen in the cases described here can be considered abnormal, and the question poses itself as to why the changes are not seen more often.

Eakin and Abbott⁴⁵ reported a case of pulmonary conus stenosis with endocardial and myocardial fibrosis in which there was intimal thickening of the coronary arterioles in the area of fibrosis.

Thoma,³⁸ in his well-known experiment, found medial thinning distal to arterial ligation. However, the process did not extend into the smaller branches of the artery. It has not been demonstrated that diminished intraluminal pressure per se will cause the intimal and medial changes found in the two presented cases.

The possibility remains that these vascular changes represent a response to chronic anoxia of the vessel wall itself and that pathologic-anatomic and experimental studies may reveal similar changes and so help to establish the pathogenesis.

SUMMARY

1. Clinical and autopsy findings are reported in two infants, aged 3 and 6 months at death, in whom the left coronary artery arose from the pulmonary artery. No additional cardiac anomalies were present. The literature is reviewed.

2. In both cases there was excessive dilatation and hypertrophy of the left ventricle, with necrosis, fibrosis, calcification, and dilated sinuses in the myocardium. There was musculoelastic thickening of the intima of some of the smaller arteries. Fibroelastic thickening of the endocardium of the left ventricle was present. It is felt that these changes are attributable to chronic anoxia of the portion of the heart supplied by the left coronary artery.

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THE PLETHYSMOGRAPHIC MEASUREMENT OF BLOOD FLOW THROUGH THE FOREPAW DURING EXPERIMENTAL SHOCK

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EVIDENCE has accumulated that in experimental shock in animals there is an active peripheral vasoconstriction which greatly decreases the blood flow through peripheral vessels.¹⁻³ This has been considered to be the cause of a prolongation of the circulation time in this condition.⁴ Similar reductions in the peripheral blood flow in the limbs of man have been reported. These reports were based on measurements with the venous occlusion plethysmograph⁵⁻⁸ and on observations of the capillary bed of the fingernail.⁹

It was felt that determination of the time course of the blood flow changes in the periphery during the development of the shocklike state and their correlation with the simultaneously recorded blood pressure changes would help explain some of the changes seen in shock. For this purpose, a venous occlusion plethysmograph, based on the principles evolved by Landowne and Katz¹⁰ for the larger plethysmograph applicable to man, was adapted for animal studies. The flow in a limb during the course of shock was determined by this means and the data were compared with the simultaneously recorded arterial blood pressure (obtained with the direct needle manometer of Hamilton and co-workers¹¹).

Plethysmograph for Use in the Dog.—The volume of the dog's forepaw is so much smaller than the volume of the human hand, leg, or forearm that a more sensitive plethysmograph is required. After considerable trial, a plethysmograph was developed which was found adequate for our purpose. Sensitivity was increased and finer adjustment of sensitivity could be made by (1) a water bladder which permits control of the air space in the plethysmograph and (2) a modification of the Frommer pressure recorder developed in this laboratory.¹² As described previously,¹² this instrument records pressure changes by means of a condenser in which one plate is fixed, while the position of the other is changed by the pressure alterations impinging upon it. For the purpose of recording the very slight pressure rise produced in the plethysmograph chamber upon obstruction of the venous flow, the variable condenser of the Frommer apparatus

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was made very sensitive by mounting the movable metal plate on a thin airtight rubber membrane; electrical contact between the metal plate and the metal tube of the condenser was maintained by a thin wire bridge. The use of the Frommer apparatus also made it possible to record the pressure rises close to the plethysmograph since the condenser head could be placed next to it, while a long flexible cable served to connect the condenser to the amplifier. The assembled plethysmograph is shown in Fig. 1.

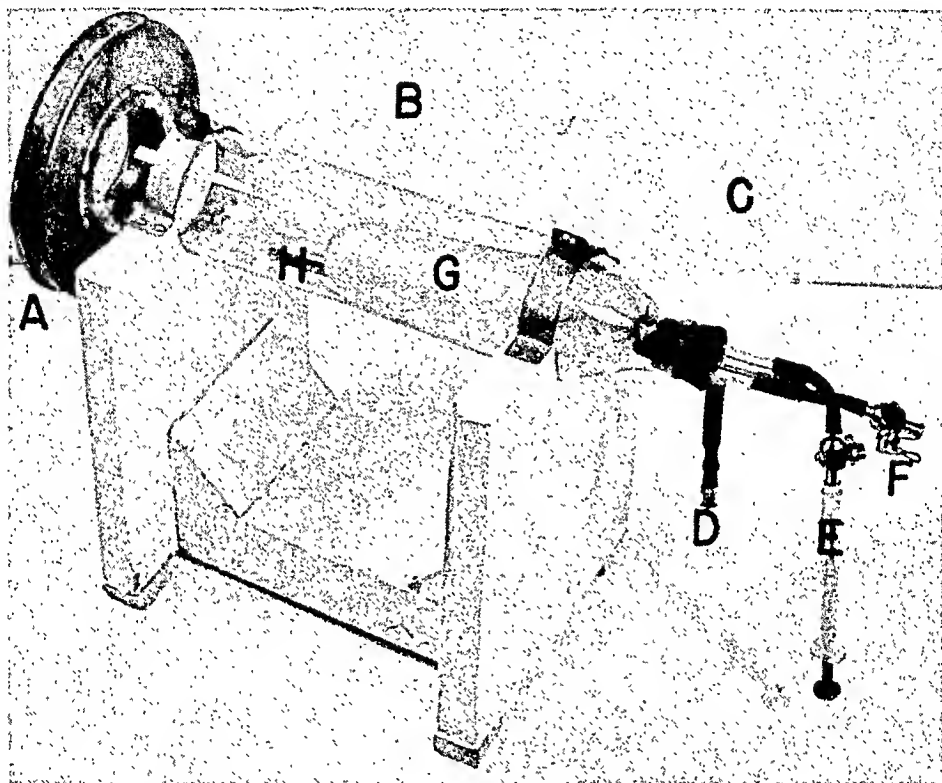


Fig. 1.—Larger glass plethysmograph assembled for use. A is the collar. B is the plethysmograph body (2 $\frac{1}{4}$ inches in diameter and 8 inches long); a smaller one (1 $\frac{1}{4}$ inches in diameter) was also used. C is the "tail." The plethysmograph consists of a 5-inch glass flange with heavy rubber tire inner tube glued to each side for cushioning effect; on the side of the flange toward the glass chamber, a metal plate is fastened to permit clamping of the metal plate diaphragm. D is the recording outlet connected to the Frommer recorder. E is a tuberculin syringe used for calibration; the stopcock above it is closed when not in use. F is the outlet to allow the pressure in the plethysmograph to reach atmospheric before a flow reading is taken; the stopcock is open except when a reading is being taken. G is the water-filled rubber bladder (a condom) employed to alter the air space in the plethysmograph for adjustment of sensitivity; this is accomplished by changing its size by adding or removing fluid through a fenestrated tube within the bladder. H is a perforated tube connected to the outlet for recording the pressure changes in the plethysmograph. The plethysmograph is constructed of glass so that the limb can be directly observed as to position, color, and state of superficial veins. In addition, it is possible to judge directly the amount of air space and the placement of the bladder, G. The latter is important in order to avoid direct contact between the bladder and forepaw. See text for further discussion.

PROCEDURE

The dog was anesthetized with nembutal (25 mg. per kilogram of body weight) and the left forepaw carefully shaved. A square of dental rubber dam was cut with a central hole 2 or 3 mm. smaller than the diameter of the paw

below the sixth callosity, which is above the humero-ulnar joint on the inner aspect of the paw. A layer of rubber cement was applied to a narrow strip of skin and to the surface of a brass plate with an opening of sufficient size to permit passage of the forepaw. The rubber diaphragm was cemented to the brass plate and both pulled over the paw to make an airtight seal on the cemented skin just distal to the sixth callosity.

The forepaw was inserted into the plethysmograph chamber and the brass ring clamped to the collar of the plethysmograph; lubricant jelly was used as a seal. The volume of paw inserted in the chamber was determined by measuring the amount of water used to fill the chamber and subtracting the value from the capacity of the chamber. Enough water was left in the chamber after draining to assure water vapor saturation. After draining off the water, the rubber bladder and the parts for recording were inserted in the opposite end of the chamber. The rubber bladder was filled with water at room temperature, the condenser head of the Frommer apparatus attached to the air outlet of the plethysmograph, and the apparatus checked for leaks. Leaks were tested for by the ability of the plethysmograph to hold pressure when small amounts of water were added to the bladder.

The venous occlusion cuff was next wound around the paw just proximal to the sixth callosity and the arterial occlusion cuff, just distal to the humero-ulnar joint. This was arranged so that it could be quickly connected to a large air pressure reservoir at the desired level. The Hamilton manometer was connected to a cannula in the left common carotid artery. All the tubes were connected, the electrical circuits closed, the recording lights turned on, and the camera started.

Next, a test for "tissue bulge artefact" was made by inflating the arterial cuff above the systolic arterial pressure (usually to about 250 mm. Hg) and then inflating the venous occlusion cuff to about 60 to 70 mm. Hg. Any shift in the plethysmographic volume observed under these conditions can only be due to movements of tissue in or out of the plethysmograph. Readjustments of the degrees of flexion and extension of the paw usually eliminated or minimized this artefact as well as the movements of the paw in and out of the plethysmograph during respiration.

Calibration of the plethysmograph was repeated before practically every record of blood flow. This was accomplished by injecting a known quantity of water into the water bladder of the plethysmograph and recording the change in pressure level.

Four to six control flow readings were obtained before injection of lampblack into the veins of both hind limbs. The technique for the latter operation was that described previously.¹³ Readings were repeated at five-minute intervals postoperatively until flow was minimal or appeared to be zero. Thereafter flow readings were taken at thirty- to sixty-minute intervals until the death of the animal. A total of five such dogs were studied. Controls were run on four other dogs who were maintained under anesthesia for a number of hours without the lampblack injection; two of these were subjected to a laparotomy and dissection of the common iliac vein.

Precautions in the Use of the Plethysmograph and Pitfalls in Its Use.—Pitfalls which can ordinarily be avoided include the following:

1. Leaks in the apparatus. These may result from a rubber diaphragm with an opening too large for the paw. Great care must be used in shaving the forepaw to avoid abrasion or skin cut which prevents the rubber cement from adhering to the skin.

2. Movements of the limb into or out of the plethysmograph (Fig. 2, A and B). These will cause movements of the base line. Extremely slow movements are not per se disturbing since the plethysmograph air outlet can be opened to bring the pressure back to atmospheric. Such slow base line movements, however, may represent changes in the quantity of blood within the forepaw. A steady increase may occur with venous engorgement when the opening in the rubber diaphragm is too tight; it is to be avoided. More rapid movements of the base line may represent respiratory artefacts or be due to too light anesthesia

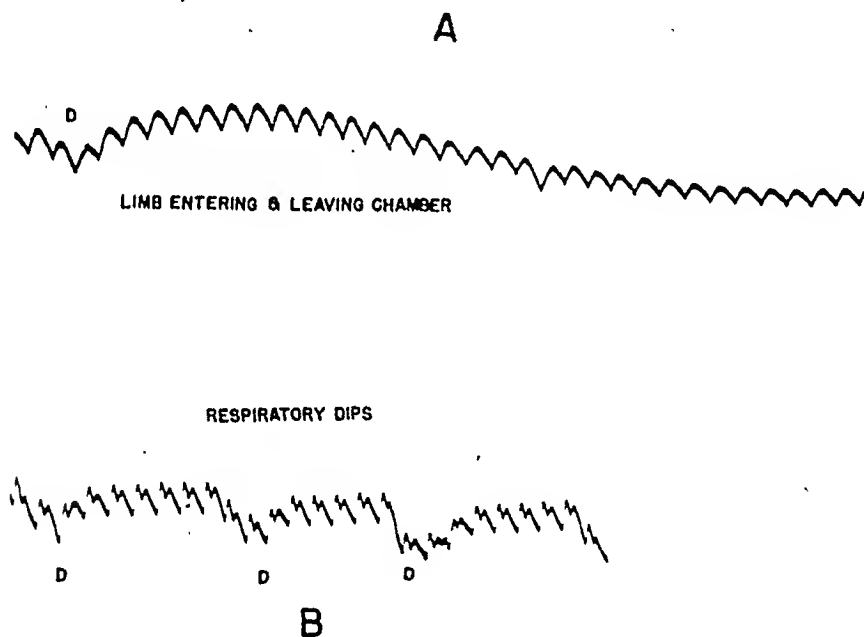


Fig. 2.—Several types of artefacts encountered with the plethysmograph. In A, a shift of the record is seen due to respiratory movement of the limb in and out of the plethysmograph (the rise and fall, respectively); superimposed on this is the volume pulse and two dips also due to respiration, the first labelled D. In B there is seen, besides the volume pulse, a number of dips, D, due to respiration; in addition, a slower downward movement of the record is present, suggesting a nonrespiratory movement of the limb out of the plethysmograph. See text for further discussion.

or poor fastening of the paw in the chamber. This can be remedied by altering the angle of flexion of the forepaw, by shifting the angle of flexion of the entire leg, by fixing the humero-ulnar joint, or by increasing the depth of anesthesia.

3. Venous occlusion artefact. This was discussed in the foregoing. In the course of an experiment it was found to lessen as the animal went into shock.

It is obvious that as the arterial pressure falls with the development of shock, the pressure used to inflate the venous cuff must be diminished in order to keep

it well below the diastolic pressure, since otherwise the inflow will be reduced and a false low reading obtained.

Recording the Blood Flow and Analysis of the Record.—The blood flow was obtained from the change in pressure in the plethysmograph chamber recorded on the photokymograph. A typical record is shown in Fig. 3. Records were checked for the presence of artefacts as discussed in the preceding section. Where present, this portion of the record was not used for reading. Excluding records with artefacts, all readings were taken during the second in which the blood flow was maximal. The vertical displacement of the pressure curve during this

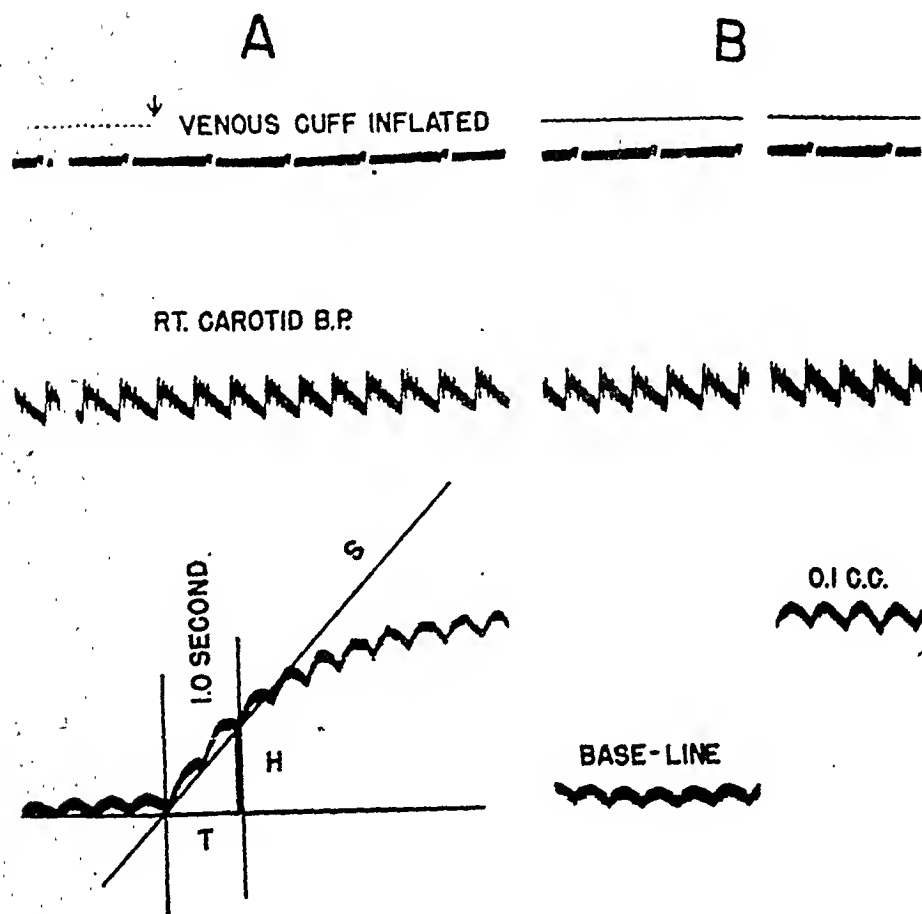


Fig. 3.—A typical record (without artefacts) for calculation of flow. In A is shown the record before and after venous occlusion marked by an arrow in the top line. The records from above down are: the record of the signal magnet which signals time of venous occlusion, time line in seconds, right carotid intra-arterial pressure curve, forepaw blood flow record. On the lower curve, the method of calculating flow is shown. S is the slope of the volume increase, T is the time interval of 1.0 second on the base line, H is the vertical height attained by S in 1 second. The calibration record is shown in B; the difference in height of the volume record in the two portions represents 0.1 c.c. See text for further discussion.

second was measured off, using homologous points of the successive pulses, and expressed as a multiple of the vertical distance between two successive calibration lines. Temperature and barometric pressure data showed small enough fluctuations to be negligible. Flow readings were converted to cubic centimeters per minute per 100 c.c. limb volume.

Several errors in reading flows from the pressure record were encountered. These are pointed out to show that the method is not as precise as desirable, a defect which this plethysmograph shares with others.

The calibration lines were found to show (1) greatly variable distances in successive calibrations, (2) at times, oscillations instead of a steady horizontal line, (3) more commonly an upward or downward slant, and (4) different increments in height for each successive tenth of 1.0 c.c. of water added. The last is due to the different sensitivity of the membrane in the different pressure regions. It need not introduce an error if the calibration distance used for conversion is chosen at the level of the portion of the record used for reading. The other disturbances were encountered much more frequently and to much greater degree before the animal went into shock. They are, therefore, probably due to tissue movement in and out of the chamber. A contributing factor to the variability of successive calibrations may be the inaccuracy of measuring 0.1 and 0.05 c.c. quantities with a tuberculin syringe. Of greater importance seems the fact that the camera was turned on after the fluid was introduced and the stopcock between syringe and water bladder closed. Tissue movement in this time interval would not be on record, yet may have caused a shift of the pressure line by the time recording started. Thus the second half of a respiratory dip might appear as an upward slant. To avoid biased reading of the records, the first portion of the calibration line was arbitrarily considered as determining the distance in all cases, since it was usually not possible to state which was the calibration level and which were the accidental deviations from it.

Another error is due to the fact that not all of the paw occluded was within the plethysmograph. The plethysmograph was below the sixth callosity and the venous cuff above it (0.5 to 1.0 cm. proximal to the collar of the cuff). Under such circumstances it is possible that redistribution of blood between the intra- and extraplethysmographic portions of the paw would change the slopes.

It is apparent that the flow determinations, especially in animals not in shock, are crude and have a large experimental error. Actual successive determinations of four to six readings three to five minutes apart showed an average variation of 31 per cent (standard deviation, 25.2) in eleven anesthetized dogs. Doubtless some of the variation was real, but much of it was due to the experimental error of the measurement. Successive determinations in animals in a state of shock usually showed very good agreement, and, of course, it was possible to determine accurately the time at which no flow could be recorded.

RESULTS

Five dogs were studied in which bilateral venous occlusion led to a shock-like state with death in $5\frac{1}{4}$, $7\frac{1}{4}$, $8\frac{1}{4}$, $8\frac{1}{2}$, and $14\frac{3}{4}$ hours. A typical experiment is shown in Fig. 4. It will be seen that the forepaw flow fell close to zero quickly within one and one-half hours, while the major fall in blood pressure and the rise in heart rate occurred later. This was representative of the four other experiments. The forepaw flow became imperceptible within one-fourth to one and three-fourths hours and to less than 1 per cent of the control flow (100

per cent being the average of four to six readings preceding the operation) within five to fifty minutes. Thus, it will be seen that the decrease in limb flow is rapid indeed. No correlation could be made between the time of survival of these dogs and the time course of the decline in forepaw blood flow.

The drop in blood pressure was more gradual. In the first hour it fell, on the average, 10 per cent below the control (even though values above control levels were observed in some dogs). This rate of fall was maintained for the next hour or two, with some acceleration of the rate depending on the rapidity with which shock became irreversible. In the last few hours of life the blood pressure dropped more and more rapidly, the heart rate accelerated greatly, and the pulse pressure declined. In the final hour these changes of blood pressure were associated with a progressive slowing of the pulse.

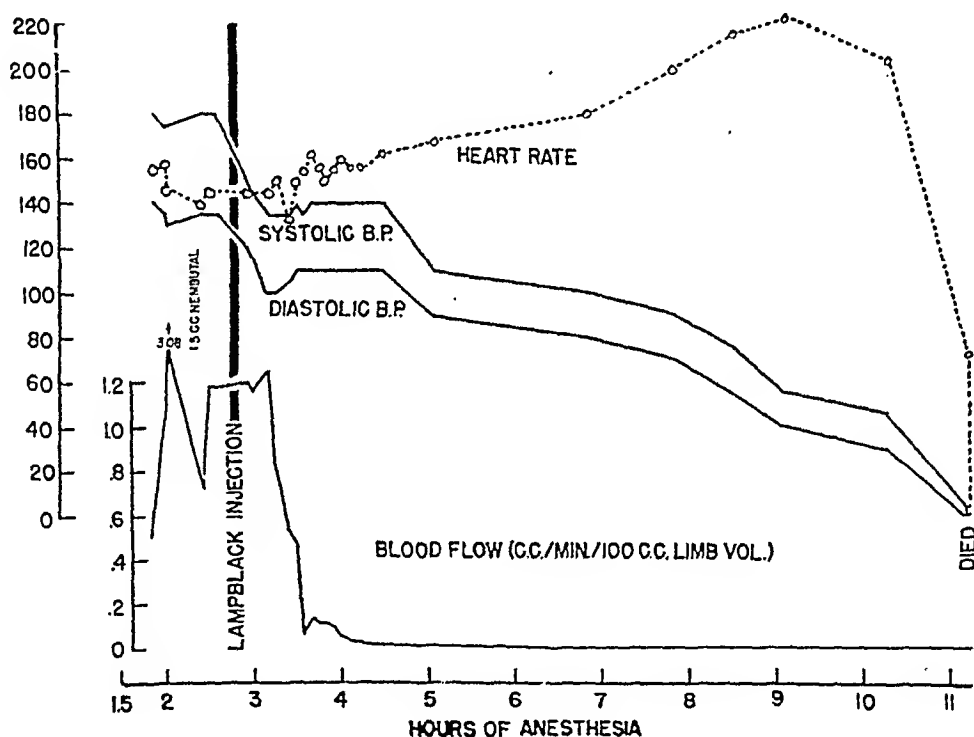


Fig. 4.—A typical experiment showing the effect of bilateral venous occlusion of the hind limbs upon the blood flow of the forepaw, the arterial blood pressure, and the heart rate. Abscissae represent hours after anesthesia was begun. The time of operation is indicated by the vertical block labelled lampblack injection. The various curves are labelled. Blood pressure is measured in millimeters of mercury; heart rate, in beats per minute. See text for further discussion.

Control studies were made on two dogs to determine the effect of protracted nembutal anesthesia. One of the experiments is shown in Fig. 5. It shows the wide variability in forepaw flow and the smaller fluctuation in blood pressure, but there was no discernible trend in the course of the experiments. Only the heart rate showed a progressive fall with time, due to the repeated injections of nembutal necessary to keep the animal immobile. Because of the progressive state of shock, it was not necessary to repeat the anesthesia in the experimental shock animals. It would appear, therefore, that the changes observed in venous occlusion shock are not due to the anesthesia employed.

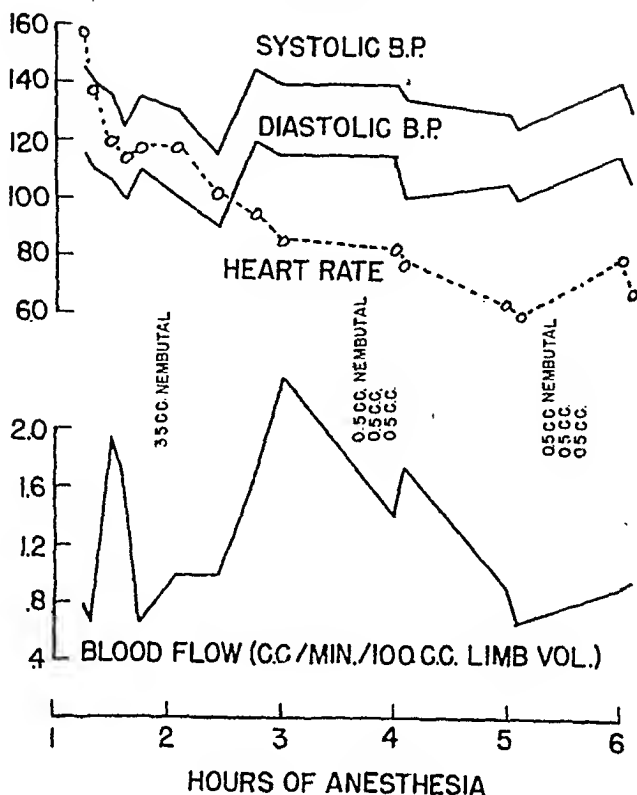


Fig. 5.—Control experiment in which the dog was kept anesthetized for six hours without other intervention. The initial dose of nembutal was 25 mg. per kilogram. Observations were begun one hour later. Abscissae represent hours after start of anesthesia. Ordinates as in Fig. 4. The time and quantity of further nembutal administration indicated above the blood flow curve. See text for further discussion.

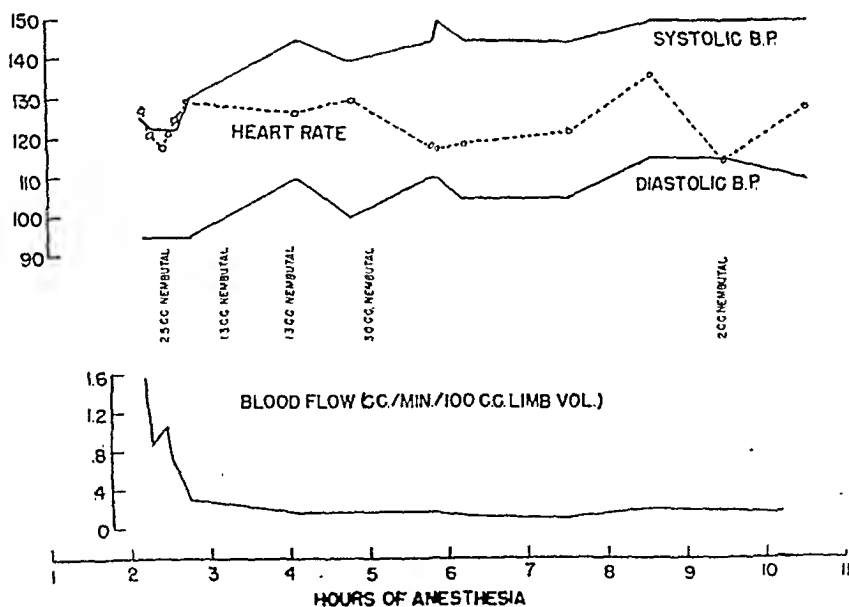


Fig. 6.—Control experiment in which the dog was kept anesthetized for eleven hours and in which a mock operation was performed just before the observations recorded in the figure. Conventions as in Figs. 4 and 5. See text for further discussion.

A second type of control was run on two dogs in which anesthesia was combined with a bilateral mock operation identical with the experimental one, but omitting ligation of veins and injection of lampblack. The observations made in one of these dogs are shown in Fig. 6. Blood flow in the forepaw declined at much the same rate as in the shock animal but remained somewhat more than 12 per cent of the control flow. The blood pressure did not drop and the heart rate remained fairly uniform. The surgical procedure obviously had a marked effect on forepaw flow but it led neither to a progressive blood pressure or heart rate change nor to an apparent complete cessation of flow. Furthermore, these animals survived beyond the period during which the experimental animals succumbed.

It is interesting to note that one animal which survived the bilateral vein occlusion showed an early drop to a near-zero flow in the forepaw. For the ten hours of observation the flow did not appear to be resumed. In this animal the blood pressure fell at first, but toward the end of the period of observation it began to rise again toward normal while the blood flow was still close to zero. The observations on this animal and on the animals with mock operations probably depict the course of events in reversible shock and in the earliest stages of shock, respectively.

DISCUSSION

Blood flow in the forepaw, which is mainly skin flow, declines very early in a condition leading to shock. A distinction is to be made between a drop in forepaw flow and apparent cessation of forepaw flow. The former occurred even in conditions such as a simple laparotomy which did not lead to blood pressure drop or other evidence of shock. Reduction of flow may thus indicate impending shock but is not a sure sign of it. Apparent zero flow in the forepaw can be considered a sign of shock, but it is not a sign of irreversible shock, as evidenced by the long-continued apparent zero flow of the forepaw, associated with a delayed drop in blood pressure, in one animal which later recovered. The first evidence of this recovery was the return of blood pressure toward normal.

Our results are in accord with the now generally recognized view that blood flow in shock in general declines before the blood pressure^{14,15} and that skin flow in particular declines to extremely low levels. Cardiac output, as indicated by heart size, begins to decrease at about the time that skin flow has apparently declined to zero.¹³ Apparently, as the amount of circulating blood declines, blood is diverted from the less vital organs to those like heart and central nervous system (respiratory center) which must continue to function if the animal is to survive.

Thus it would appear that the decrease in peripheral flow, surely in skin flow, is a compensatory mechanism. That the skin flow appears to reach zero so early in shock means that the compensatory vasoconstriction in this region is brought into play very quickly and to its utmost extent.

Tachycardia develops much later than the drop in skin flow and is progressive, while the drop in skin flow is early and apparently complete. Since both the skin vasoconstriction and the tachycardia are doubtless chiefly reflex in origin, it is of interest that the timing and pattern of these two phenomena are so different.

If these results can be applied to man, a pale and cold skin, the sign of skin vasoconstriction in man, should be viewed as an *early* sign of impending shock (obviously a pale cold skin occurs in other circumstances).

Our results also suggest an explanation for the detrimental effect of heat application reported in shock.¹⁶ If the reduction of skin flow close to zero is a compensatory mechanism in shock, then heat applied to the body should be avoided for it would lead to release of the vasoconstriction and divert blood from more vital organs to the skin.

SUMMARY

1. The skin flow of the forepaw of the dog was studied in a standardized type of experimental shock (following venous occlusion of the hind limb).
2. A small animal plethysmograph used for this purpose is analyzed.
3. The results indicate that the blood flow in the forepaw apparently falls to zero very early in the development of the shocklike state. Furthermore, this drop in blood flow occurs much earlier than the fall in blood pressure or the increase in heart rate.
4. Anesthesia per se does not affect the blood flow. Mock operations reduce the blood flow but do not suppress it.
5. A physiologic correlation between the peripheral blood flow, arterial blood pressure, and heart rate in the development of the shocklike state is discussed.

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ON THE MECHANISM OF PAROXYSMAL TACHYCARDIA WITH RHYTHMIC ALTERNATION IN THE DIRECTION OF THE VENTRICULAR COMPLEXES

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PAROXYSMAL ventricular tachycardia is uncommon, although with the increasing number of electrocardiograms being taken, it is now being detected more frequently. The so-called bidirectional type, or paroxysmal ventricular tachycardia with rhythmic alternation in direction of the ventricular complexes, is even more uncommon. In the past thirty years at the Rhode Island Hospital electrocardiograms have been obtained in twenty-eight patients with paroxysmal ventricular tachycardia. Only one of these has shown the bidirectional type. This case is reported because of the interesting clinical and electrocardiographic findings which bear on the underlying mechanism. The discussion will be limited to the bidirectional alternating type of ventricular tachycardia.

REVIEW OF THE LITERATURE

In 1911, Levy and Lewis,¹ working on cats which were exposed to low tension chloroform vapor, produced an irregular tachycardia caused by ventricular extrasystoles which were thought to originate in multiple foci. From time to time they obtained tracings showing a ventricular tachycardia in which the complexes alternated in direction. They felt that this configuration was the result of premature contractions alternately generated in separate foci. Small intravenous injections of adrenaline chloride given to cats under the influence of low tension chloroform vapor caused these irregularities to progress ultimately into ventricular fibrillation.

The first example of regular alternation of upward and downward deflections in man was published by Schwensen² in 1922. He reported on two patients with ventricular tachycardia, both of whom had received digitalis. The first showed coupling due to ventricular extrasystoles and the second patient, who had rheumatic heart disease with auricular fibrillation, showed paroxysms of bidirectional ventricular tachycardia. Schwensen discussed the possibility of this being due to hyperirritability of the ventricle resulting from the administration of digitalis.

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Similar cases were subsequently reported by Felberbaum,³ Reid,⁴ Luten,⁵ Clerc and Levy,²¹ Marvin,⁹ Clarke,¹² Schwab,¹⁵ Howard,¹⁶ and Piloni,¹⁷ in all of which digitalis was thought to play an important etiologic role.

Sherf and Kisch¹⁸ reported their observations of eighteen cases of paroxysmal ventricular tachycardia which they divided into three types: (1) ventricular tachycardia with regular rhythm and the alternation of two kinds of ventricular complexes (Type I); (2) ventricular tachycardia with an alternation of two types of ventricular complexes and an alternation of a longer and shorter diastole (Type II); (3) ventricular tachycardia in which the shape of the ventricular complexes as well as the length of diastole changed irregularly (Type III). Three of their patients on whom data were published showed the typical alternating bidirectional ventricular complexes. Fourteen of their eighteen patients were receiving digitalis when the tachycardia appeared. They concluded that the quantity of digitalis administered is not a factor of exclusive importance and that the condition of the myocardium is a more important factor.

Recently, Braun and Wosika¹⁹ reported another case in a 68-year-old man with auricular fibrillation and congestive failure. On two occasions this patient developed bidirectional ventricular tachycardia following the use of *Digitalis purpurea*. Strophanthin and *Digitalis lanata* produced no toxic effects. The patient was improved on discharge from the hospital.

Gilchrist⁷ reported five cases of paroxysmal ventricular tachycardia. In one patient (Case 4) a rhythmic alternation in direction of complexes was seen for a few cycles at the beginning of the record. Nicotine intoxication was regarded as important in the production of the arrhythmia in this particular patient.

Orsi and Villa¹⁰ reported on one patient in whom a change from the usual type of ventricular tachycardia to the alternating bidirectional form occurred a few seconds following the intravenous injection of calcium chloride.

Additional cases have been reported by Smith,¹¹ Strauss,¹³ Langeron,¹⁴ Gallavardin,⁶ and Palmer and White.⁸ Howard²⁰ reviewed the tachycardias due to digitalis without adding any new case of the bidirectional alternating type.

Several theories have been advanced to explain the phenomenon of the alternating complexes of ventricular tachycardia. Two possibilities were recognized by Schwensen,² Felberbaum,³ and Luten.⁵ One was that the origin of the impulses was in a single focus above the bifurcation of the bundle of His and the alternating direction was the result of alternating conduction through the right and left bundle branches. The second was that the impulses originated within the ventricles and that they were generated alternately in the right and left chambers.

Gallavardin⁶ was the first to suggest the possibility of circus movement in the ventricles as an explanation for this unusual type of tachycardia. Palmer and White⁸ rejected the explanation that all ventricular impulses arose in one focus located above the bundle of His, because they found an alternation of the length of diastole in two of their patients. After discussing such possible mechanisms as parasystole and re-entry, these authors suggested that the phenomenon was due to a double ventricular circus movement.

Howard¹⁶ suggested that "The mechanism depends upon a relatively fixed delay in conduction time of one branch of the bundle, while the conductivity of the other branch waxes and wanes so that it alternately exceeds and fails to equal that of the first branch."

Scherf and Kisch¹⁸ attempted to show that in every one of their three types, a single center of stimulus formation may exist, while the abnormal picture may be caused simply by a disturbance of intraventricular conduction. Braun and Wosika¹⁹ concluded that "The assumption that multiple ectopic foci are present in the damaged myocardium and are responsible for this alternating paroxysmal tachycardia cannot be avoided. The height of the paroxysm may be the result of interference phenomena, or of the predominance of two centers of the same order over the other ectopic foci."

Summary.—Including the case to be discussed herewith, thirty-two cases have been reported in which alternating bidirectional ventricular tachycardia has been observed. These include instances of continuous alternation in the direction of the complexes and instances in which only brief groups of alternating bidirectional ventricular complexes were recorded.

Of these thirty-two patients, twenty-six died soon after the arrhythmia was discovered, one lived twenty-five days after its onset, our patient lived seventy-two days after its onset, and one patient lived five months after the disturbance first appeared. The patient reported by Braun and Wosika was still living twenty-seven months after the attack of alternating bidirectional ventricular tachycardia. One patient was improved on discharge and one returned to work but could not be traced subsequently.

Excluding three of Gallavardin's patients in whom it is uncertain whether digitalis was administered, all but two of the patients received digitalis. The patient reported on by Orsi and Villa showed alternating bidirectional ventricular tachycardia a few seconds following an intravenous injection of calcium chloride. The patient previously had received ouabain intravenously. In one patient, nicotine intoxication was thought to be the exciting factor.

CASE REPORT

W. S., a 57-year-old man of Italian descent, was admitted to the Rhode Island Hospital Oct. 7, 1945.

Present Illness.—The patient had known that he had hypertension for several years. Cardiac symptoms had been present for about eighteen months. Seven months before admission he had become extremely weak, short of breath, and unable to continue his work. He was given digitalis and continued to take a maintenance dose of 0.1 Gm. daily. He had occasional severe attacks of dyspnea and at such times he increased the digitalis dosage to 0.2 or 0.3 Gm. daily. He became progressively worse and his attending physician sent him to the hospital. The past medical history, family history, and review of the systems were irrelevant.

Physical Examination.—The temperature was 101.0° F.; pulse rate, 130; and respiratory rate, 32 per minute. The patient was in severe congestive failure with dyspnea, orthopnea, and generalized anasarca. The cardiac rhythm was regular with occasional extrasystoles. The maximum apical impulse was 2.5 cm. to the left of the midclavicular line. There were no murmurs. The blood pressure was 200/110.

It was noted that paroxysms of tachycardia were occurring intermittently. At such times the heart rate was very rapid and regular and the patient complained of palpitation. Carotid sinus pressure terminated these attacks immediately. An electrocardiogram, taken in the morning of Oct. 8, 1945 (Fig. 2), showed the paroxysms to consist of bidirectional, alternating ventricular tachycardia, which was recorded in several tracings. A thoracentesis was performed and 1,225

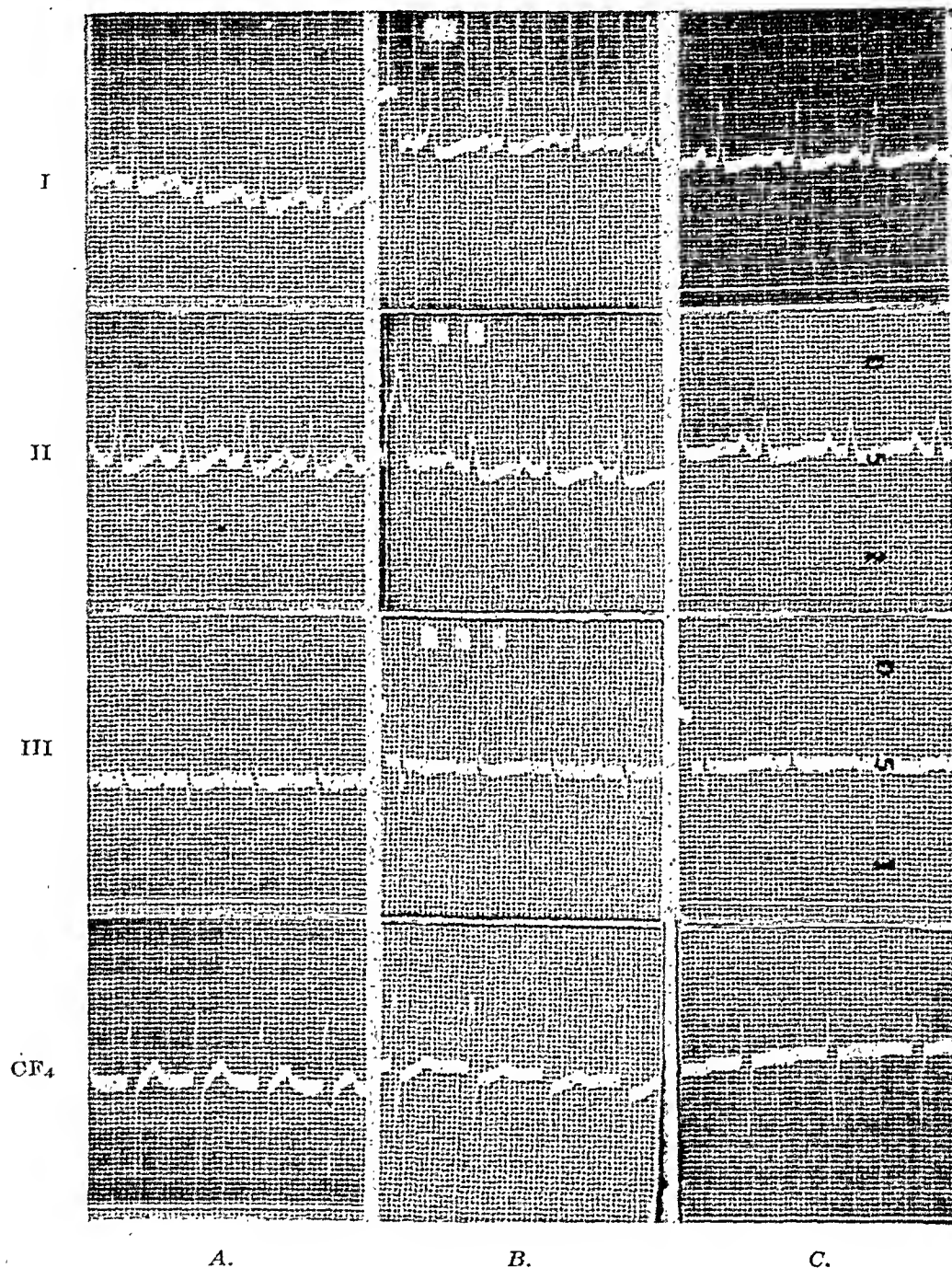


Fig. 1.—Leads I, II, III, and CF₄. A, Electrocardiogram taken before admission. B, A tracing taken October 9. C, A record taken November 13. Later tracings showed no changes.

c.c. of clear fluid was obtained. Following this, an electrocardiogram, taken in the afternoon of Oct. 8, 1945 (Fig. 5), differed considerably from the one taken in the morning. Auricular fibrillation was present together with a marked degree of A-V block and an idioventricular rhythm. On Oct. 9, 1945, an electrocardiogram (Fig. 1, B) showed a regular sinus rhythm with a rate of

109 per minute. He had no further episodes of tachycardia that were noted clinically while in the hospital.

Laboratory Studies.—The blood urea nitrogen was 20 mg. per cent; blood sugar, 102 mg. per cent; and blood cholesterol, 208 mg. per cent. Urinalysis showed a specific gravity of 1.007 with a 1 plus protein. Blood examination showed erythrocytes, 5,583,000; white blood cells, 10,150, and hemoglobin, 12.4 grams. Differential count was 84 per cent neutrophils, 12 per cent lymphocytes, and 4 per cent monocytes.

Diagnosis.—The diagnosis was arteriosclerotic and hypertensive cardiovascular disease, cardiac decompensation, bilateral hydrothorax, and bidirectional alternating ventricular tachycardia.

Clinical Course.—After the first thoracentesis, the patient was placed in an oxygen tent where he was less dyspneic. He was given 0.2 Gm. of quinidine sulfate four times daily. Ammonium chloride and mercupurin were also administered with good effects. A second thoracentesis was performed October 15 and 800 c.c. of fluid obtained. On October 26, 490 c.c. of fluid was removed. With this therapy, the patient improved slowly and the edema diminished. Digitalis was discontinued on admission.

On Nov. 17, 1945, the patient sat up in a chair and felt much stronger. The heart rhythm was regular and the rate varied between 84 and 90 per minute. The blood pressure was 140/90.

An electrocardiogram taken Nov. 13, 1945 (Fig. 1, C) showed normal sinus rhythm with a rate of 86 per minute. The conduction time was slightly increased. The P waves were prominent in Leads I and II. The T waves in Lead IV were still small. The S-T intervals were slightly depressed in Leads I and II.

On Nov. 19, 1945, the patient returned to his home where treatment included quinidine sulfate, four times daily. He remained in bed but his condition became progressively worse. He died thirty-two days after discharge from the hospital. No autopsy was performed.

DISCUSSION

The appearance of regular alternation in the direction of the complexes in ventricular tachycardia has been associated with severe cardiac damage and pathologic changes in the heart. The prognosis is usually very poor.

In the total series of thirty-two patients, excluding the patient of Clerc and Levy²¹ because the case report was not clear, the diagnoses were as follows: Arteriosclerotic heart disease with aortic stenosis, 1; arteriosclerotic and hypertensive heart disease, 9; coronary thrombosis, 2; chronic myocarditis, 2; coronary sclerosis without hypertension, 4; syphilitic heart disease, 5; rheumatic heart disease, 4; uremia, 1; tuberculous myocarditis, 1; cardiac enlargement of unknown etiology, 1; and no heart disease, 1.

Cardiac asthma occurred in four patients, anginal failure in one, and congestive failure in twenty-six. Auricular fibrillation was observed in fifteen of the thirty-one patients.

The age distribution was 16 to 80 years and averaged 55.9 years. There were eleven women and twenty men in the series.

In none of the reported cases has it been possible to prove convincingly which type of mechanism is responsible. We wish to offer an explanation of the mechanism of the peculiar type of ventricular tachycardia which occurred in our patient. We believe that both clinical and electrocardiographic evidence indicate that there were two separate foci functioning, one in the supraventricular A-V nodal tissue and the other in the ventricles.

In this patient, every episode of tachycardia could be terminated abruptly by carotid sinus pressure. The tachycardia was demonstrated by the electrocardiograms to be the type designated as bidirectional alternating ventricular tachycardia. Pressure over the carotid sinus on either side was equally effective. A record of the effect is shown in Fig. 4.

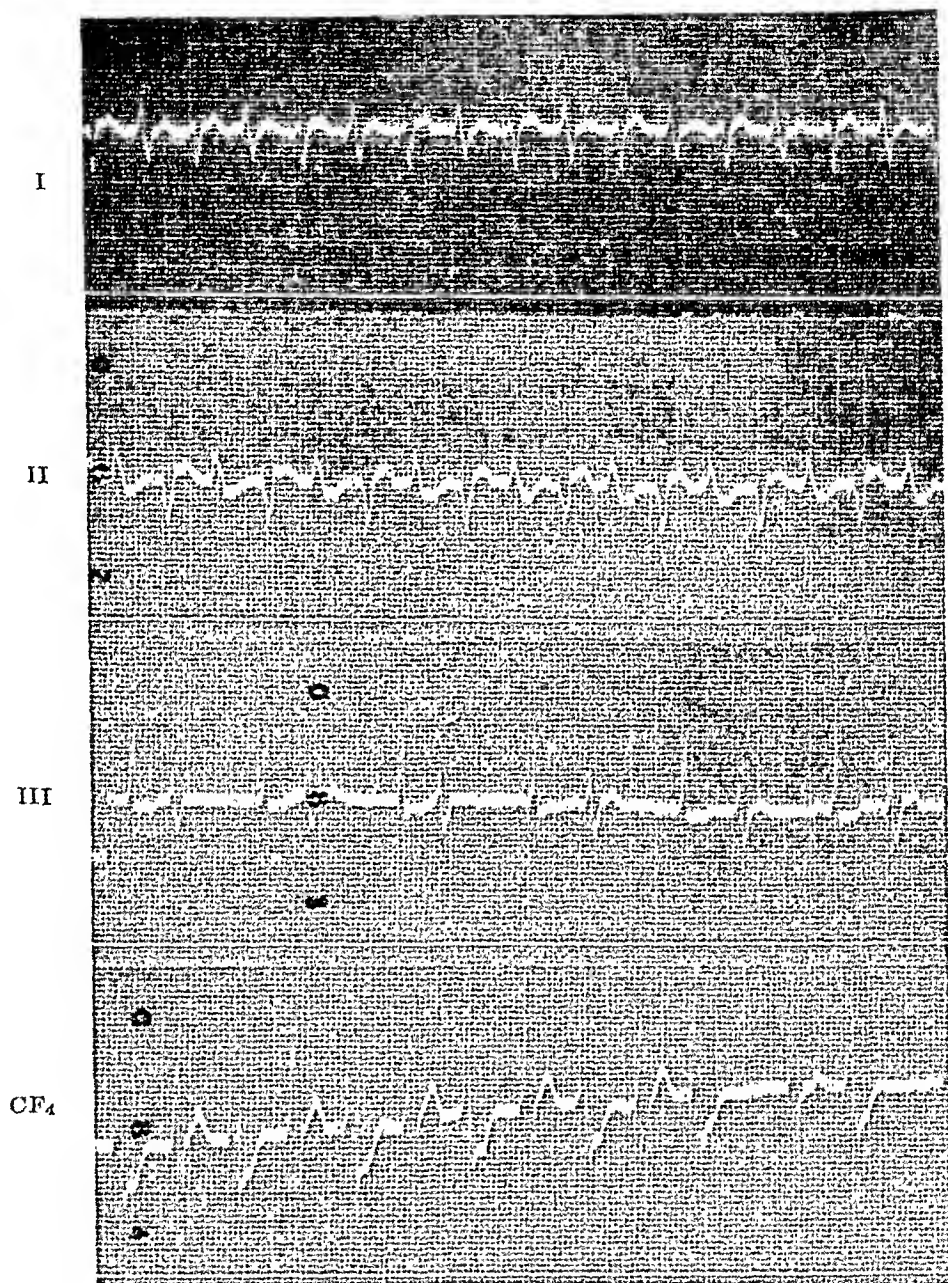


Fig. 2.—Leads I, II, III, and CF₄. Bidirectional alternating tachycardia. The interval following the upright complex is longer by 0.04 second than the interval between the downward complex and next upright complex. Lead III shows coupled rhythm following carotid sinus pressure.

It is known that increased vagal tone will stop supraventricular tachycardia, but it is thought that such stimulation has no effect upon ventricular tachycardia. Fibers from the right vagus nerve terminate around ganglion cells in auricular tissue in the immediate neighborhood of the sinoauricular node. The left vagus nerve establishes a similar relationship with the auriculoventricular node.

In mammals the vagus nerves exert their effect upon the heart through their action on the auricular muscle and the junctional tissues. They exert no direct effect upon the ventricular muscle. If the A-V bundle is severed, vagal stimulation is then without effect upon the ventricular rate.²³

Fig. 1 shows electrocardiograms taken on several occasions. *A*, a tracing taken before hospital admission, shows regular sinus rhythm with a P-R interval of 0.20 second. The S-T intervals in Leads I and II are depressed. The T waves are small and diphasic in the limb leads and upright in Lead CF_4 : Left axis deviation is present. *B* shows a record taken October 9. It is quite similar to the previous one, except that the S-T segments in Lead CF_4 are depressed. *C* shows a record taken November 13. The rate is slower. The P waves are prominent in Leads I and II. The T waves in Lead CF_4 are smaller and the S-T segment is isoelectric.

Fig. 2 shows the bidirectional alternating ventricular tachycardia. The interval following the upright complex is longer by 0.04 second than the interval between the downward complex and the next upright complex. Smith¹¹ found the same to be true in his patient. Palmer and White⁸ found the interval following the inverted complexes to be longer than that occurring after the upright complexes. Lead III was taken following carotid sinus pressure. It shows coupled rhythm.



Fig. 3.—Lead II. The beginning of a paroxysm of bidirectional alternating tachycardia. Description in text.

Fig. 3 shows the beginning of one of the patient's paroxysms of bidirectional alternating ventricular tachycardia (Lead II). In the first part of the strip there is a coupled rhythm produced by ventricular extrasystoles. The deflection time increases from 0.07 to 0.10 second in the upward-directed beats of the tachycardia.

Fig. 4 (Lead III) shows the ending by carotid sinus pressure of the bidirectional alternating tachycardia. Carotid sinus pressure is indicated by *X*. This is followed by two downward deflected complexes in succession and establishment of a rhythm in which no auricular waves are seen. In the bottom strip this rhythm is quite regular. The extrasystoles in the coupled rhythm very closely resemble the complexes in the tachycardia that are directed downward. Carotid sinus pressure abolished the upward complexes which must have originated in the nodal tissues. The auricular pacemaker then resumed its function, while the

ectopic foci in the ventricles still exerted themselves at times. In some instances these ventricular beats follow the dominant beats at a fixed interval and in other instances they occur at different times during the cycle.

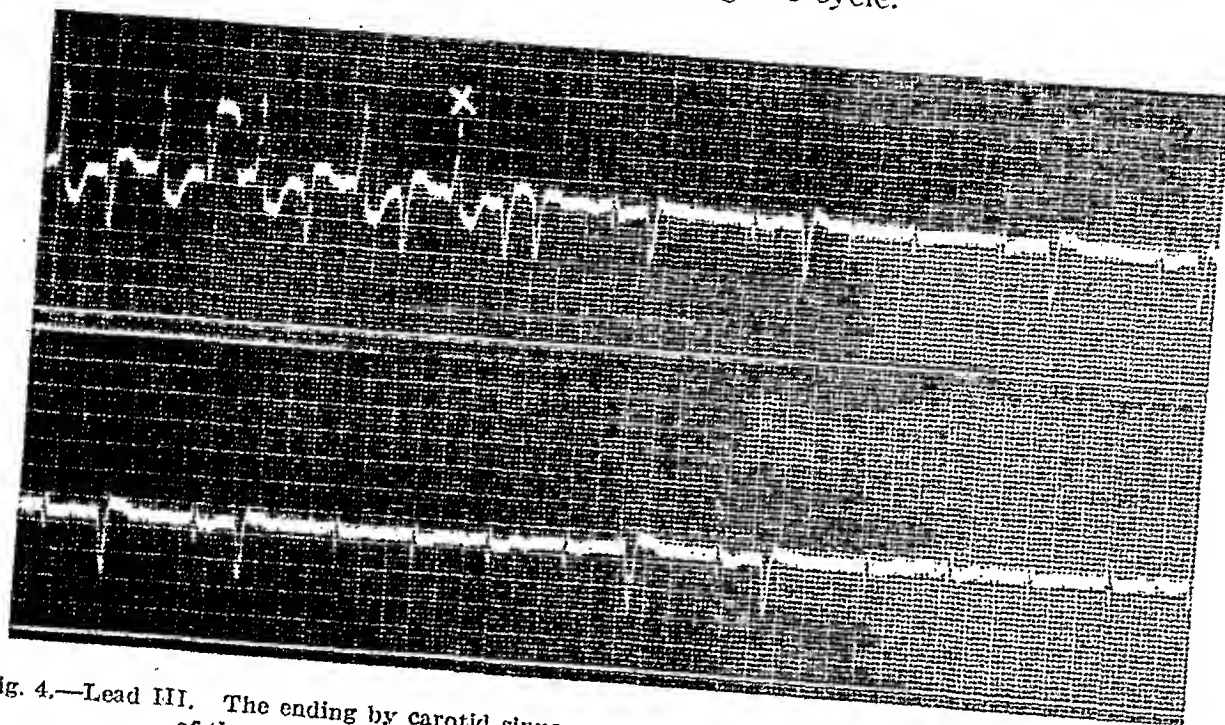


Fig. 4.—Lead III. The ending by carotid sinus pressure of the rhythmic alternation in the direction of the ventricular complexes. Carotid sinus pressure is indicated by X.

Fig. 5 is a continuous record of Lead II taken between the patient's attacks of bidirectional alternating tachycardia. It shows auricular fibrillation with complete A-V heart block. In the first strip, at the beginning, the rate of the ventricles is 100. This slows to about 93 per minute. In the second and third strips there are frequent extrasystoles appearing in different parts of the cycle. Since the QRS complex is normal in duration, the idioventricular rhythm apparently arises in the A-V node. A similar tracing has been published by Katz.²²

Most of the reported cases have been associated with digitalis and some of the patients received toxic doses of digitalis. It is known that digitalis acts on the junctional tissue to slow conductivity. It is also known that digitalis causes ventricular ectopic beats as an early manifestation of intoxication and the ectopic beats may be increased in frequency until regular coupled rhythm is produced by continued administration of the drug.

Marvin⁹ stated that in his patient, "careful consideration of the doses and circumstances in which they were used leaves the impression that there are probably factors other than the total amount of digitalis which may be responsible for the onset of the mechanism under discussion." Schwab¹⁵ concluded that the role of digitalis as an exciting factor in the causation of ventricular tachycardia was much more apparent after a study of the reported cases of the alternating type. Especially of interest is the patient reported on by Braun and Wosika¹⁹ in whom *Digitalis purpurea* brought on attacks of bidirectional ventricular tachycardia. These disappeared after strophanthin and *Digitalis lanata* were substituted. Digitalis may act in these patients with already damaged tissues to

depress the conduction system until a nodal pacemaker suddenly takes over. It is also of interest to observe that many of the reported cases were associated with auricular fibrillation and periods of coupling before the abnormal rhythm occurred. In Fig. 3 is shown the transition from the bigeminal rhythm into the bidirectional tachycardia in our patient. It is conceivable that digitalis causes a high degree of A-V block in reported patients, leaving some part of the nodal tissue suddenly to assume control along with an ectopic focus in the ventricles and produce this abnormal pattern of bidirectional alternating tachycardia. Though this is purely speculative, we do believe that the mechanism of production causing the arrhythmia in our patient is clear. Because of the instant remarkable re-

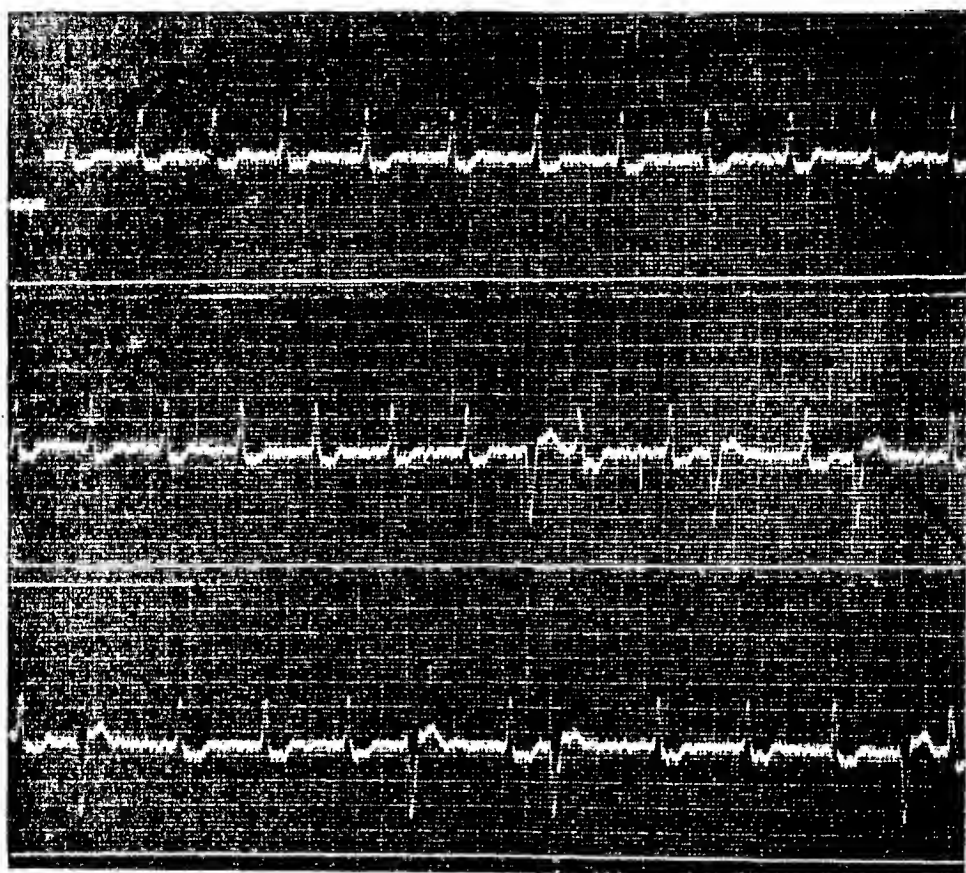


Fig. 5.—Lead II. Portions of a continuous tracing taken between the patient's attacks of alternating bidirectional tachycardia. Description in text.

sponse to carotid sinus stimulation with the resultant electrocardiographic findings, it is evident that there were two foci functioning, one in the tissues responsive to vagus stimulation and the other in tissues not responsive. We believe, therefore, that in our patient there were two distinct sites from which the impulses originated: one in the bundle of His above the bifurcation of the bundle and the other in an ectopic focus in the ventricles. If our observations are correct, we also suggest that this arrhythmia be described not as paroxysmal bidirectional ventricular tachycardia, but as paroxysmal tachycardia with rhythmic alternation in the direction of the ventricular complexes.

SUMMARY

1. A case of paroxysmal tachycardia with rhythmic alternation in the direction of the ventricular complexes in the electrocardiogram is reported together with a review of the literature.

2. There have been thirty-two cases of bidirectional alternating ventricular tachycardia recorded in the literature, most of these associated with severe cardiac damage and digitalis administration.

3. We have presented clinical and electrocardiographic evidence which suggests that in our patient the mechanism was due to the action of two separate foci, one in the A-V nodal tissues above the bifurcation of the bundle of His the other in the ventricular muscle.

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THE HEART IN ACUTE ANTERIOR POLIOMYELITIS

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THE occurrence of acute myocarditis incident to severe infection is classically exemplified in rheumatic fever and in diphtheria. Certain viral infections, including mumps¹ and influenza,² have been incriminated rarely as a cause of acute myocarditis. Saphir and Wile³ demonstrated the presence of focal perivascular and diffuse interstitial cellular invasion in the heart in six of seven fatal cases of poliomyelitis. Myocarditis was not suspected clinically in any of these patients, although, in retrospect, suggestive features were present: rapid, feeble pulse, diminished blood pressure, tachycardia out of proportion to the temperature, and cyanosis. Peale and Lucchesi⁴ found microscopic evidence of myocarditis in five of seven fatal cases of poliomyelitis. The changes consisted of vascular, perivascular, and interstitial cellular infiltration. Myocarditis had not been considered before the death of these patients.

The undeniable presence of acute myocardial changes in a high percentage of fatal cases of poliomyelitis suggested to us the advisability of careful cardiac studies in patients suffering from this disease. Our report is based upon the evaluation of 467 patients with acute poliomyelitis admitted to the Philadelphia Hospital for Contagious Diseases from 1943 to 1945 inclusive. Patients with histories suggesting pre-existing heart disease were excluded from the study.

CLINICAL OBSERVATIONS IN 456 PATIENTS WITH NONFATAL POLIOMYELITIS

The clinical findings in 456 patients with nonfatal poliomyelitis were analyzed (Fig. 1).

Murmurs.—There were 34 (7.5 per cent) mitral and 7 (1.5 per cent) aortic systolic murmurs which were recorded upon admission of the patients to the hospital. As there have been few references made to these murmurs during subsequent examinations, their clinical course is unknown.

Arrhythmias.—Sinus tachycardia with a rate above 140 per minute, and definitely disproportionate to the body temperature, was observed in 9 cases

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(2.0 per cent). Extrasystoles were noted clinically in only 3 cases (less than 0.01 per cent).

Cardiac Enlargement.—On clinical examination, the heart was found to be enlarged in 2 patients (less than 0.01 per cent). One of these had associated electrocardiographic abnormalities; a tracing was not obtained in the other patient.

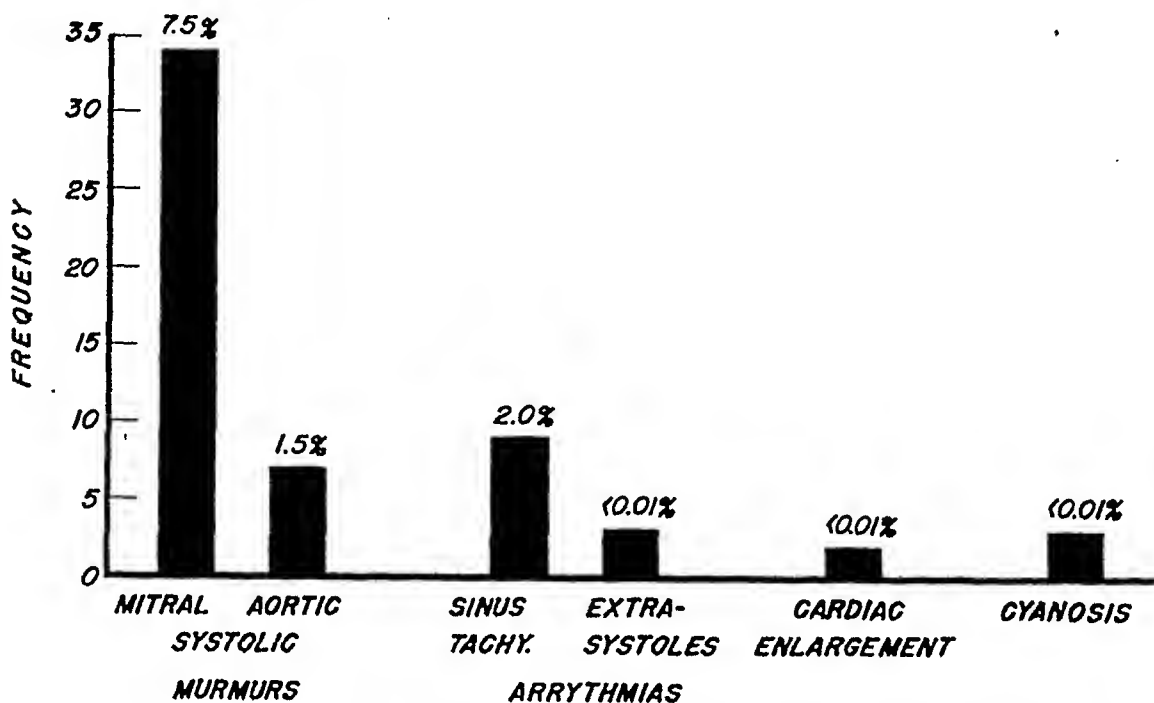


Fig. 1.—Distribution of clinical observations in 456 nonfatal cases of poliomyelitis.

Cyanosis.—Cyanosis, which required the use of the respirator, was present in 3 patients (less than 0.01 per cent). Because of their critical condition, electrocardiograms were not taken.

ELECTROCARDIOGRAPHIC OBSERVATIONS

Electrocardiograms were analyzed in 226 of the 467 patients with acute poliomyelitis (Fig. 2) and were not obtained in the remaining patients. In 32 (14.2 per cent) of the 226, the electrocardiographic pattern was abnormal.

Sex.—The electrocardiograms were abnormal in 15 (12.2 per cent) of 123 male patients and in 17 (16.5 per cent) of 103 female patients (Fig. 3). There is no significant relationship between abnormal electrocardiograms and sex.

Age.—The incidence of abnormal electrocardiograms in the various age groups (Fig. 4) was as follows: 1 to 3 years, 4 (17.4 per cent) in 23 cases; 4 to 6 years, 3 (6.7 per cent) in 45 cases; 7 to 9 years, 8 (17.4 per cent) in 46 cases; 10 to 12 years, 5 (13.1 per cent) in 38 cases; 13 to 15 years, 4 (13.8 per cent) in 29 cases; 16 to 18 years, 4 (16.7 per cent) in 24 cases; 19 to 46 years, 4 (19.0 per cent) in 21 cases. The uniform scattering of abnormal tracings in the different age groups

indicates that the age of the patient is not a significant factor in the incidence of abnormal electrocardiograms in acute poliomyelitis.

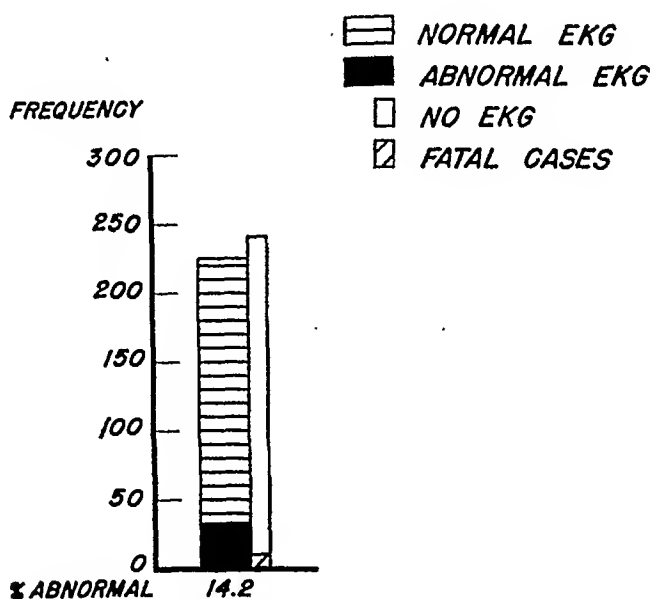


Fig. 2.—Distribution of 226 electrocardiograms in 467 cases of poliomyelitis.

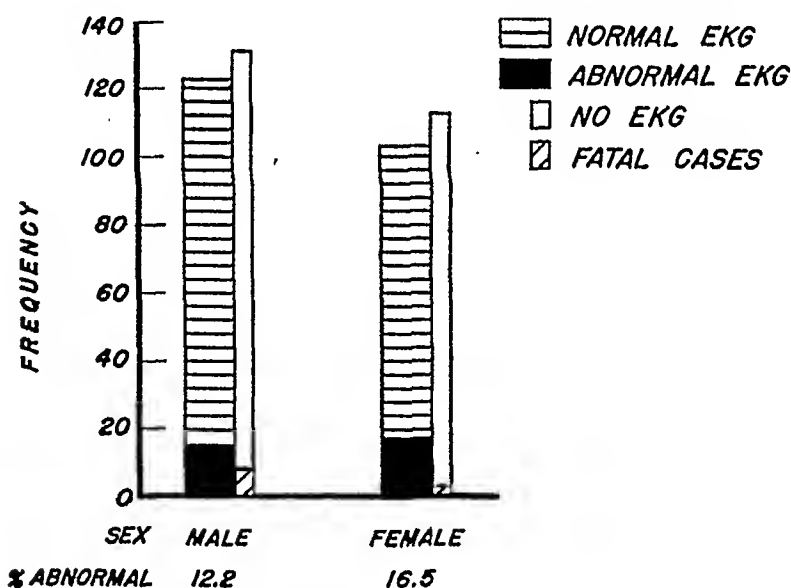


Fig. 3.—Distribution of 226 electrocardiograms in 467 cases of poliomyelitis according to sex.

Severity of Disease.—An arbitrary classification of poliomyelitis based upon the severity of the disease was devised:

- Grade I—Nonparalytic type
- Grade II—Involvement of one extremity
- Grade III—Involvement of two or more extremities, bladder, or diaphragm
- Grade IV—Bulbar or bulbospinal involvement

The cases were distributed according to this classification in order to determine the relationship between abnormal electrocardiograms and the severity of the disease (Fig. 5). The incidence of abnormal tracings was found to be

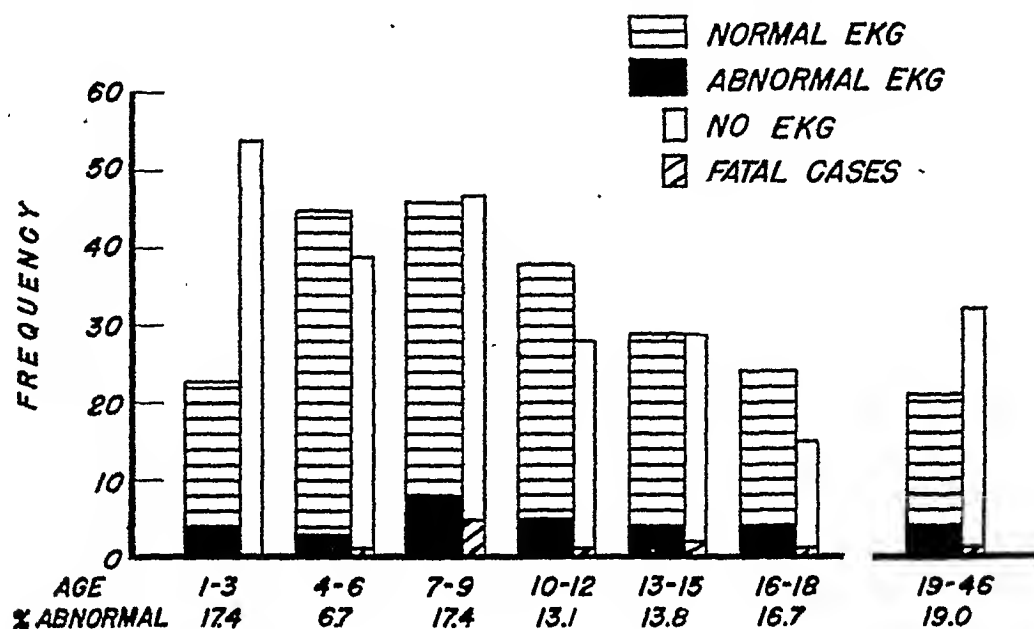


Fig. 4.—Distribution of 226 electrocardiograms in 467 cases of poliomyelitis according to age of patient.

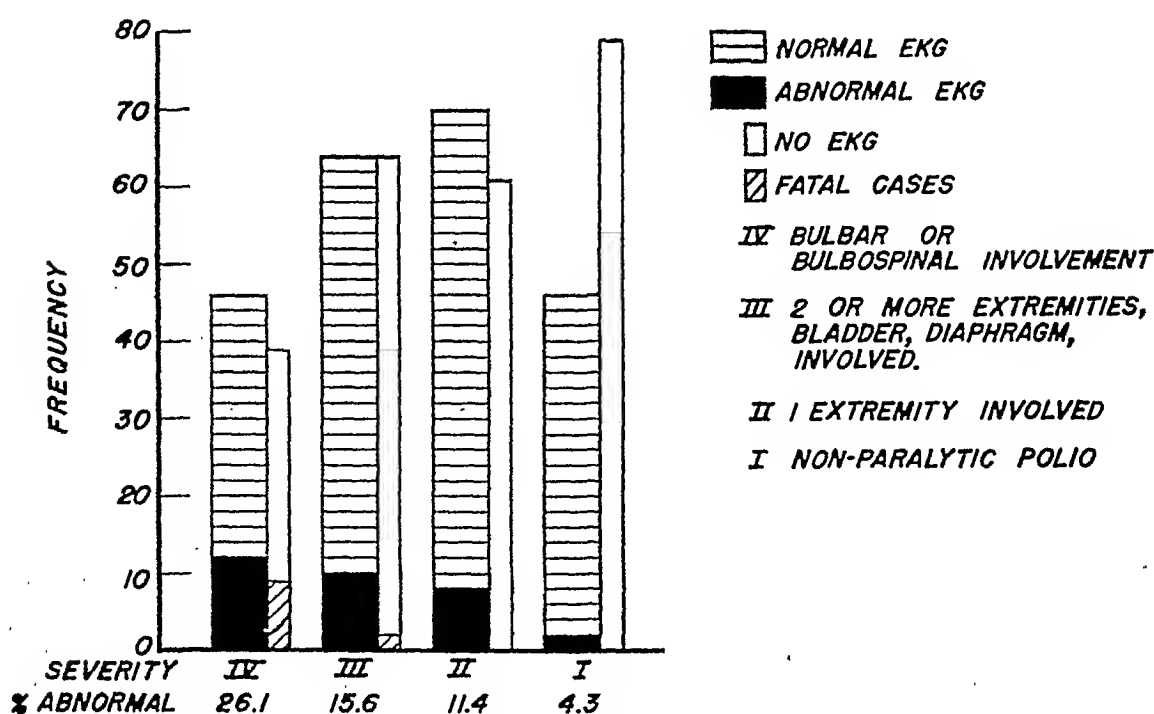


Fig. 5.—Distribution of 226 electrocardiograms in 467 cases of poliomyelitis according to severity of disease.

12 (26.1 per cent) in 46 cases of grade IV severity; 10 (15.6 per cent) in 64 cases of grade III severity; 8 (11.4 per cent) in 70 cases of grade II severity; and 2 (4.3 per cent) in 46 cases of grade I severity. The frequency of abnormal electrocardiograms rises significantly with increasing severity of the disease. This

is to be expected when one considers the uniformly high incidence of myocardial changes noted microscopically in fatal cases of poliomyelitis which are usually of grade III or grade IV severity.

Days of Fever.—Fig. 6 shows the distribution of the tracings according to the duration of the febrile period of the patients. Of 42 patients who were afebrile during their entire illness, 3 (7.1 per cent) had abnormal electrocardiograms. There were 8 patients who were febrile from one to three days; 1 (12.5 per cent) had an abnormal tracing. Forty-nine patients had fever for four to six days and 7 (14.3 per cent) showed electrocardiographic abnormalities. Of 59 patients who were afebrile after seven to nine days of illness, 7 (11.9 per cent) showed abnormal patterns. Twenty-seven patients were afebrile after ten to twelve days; 1 (3.7 per cent) of this group had an abnormal electrocardiogram. Four-

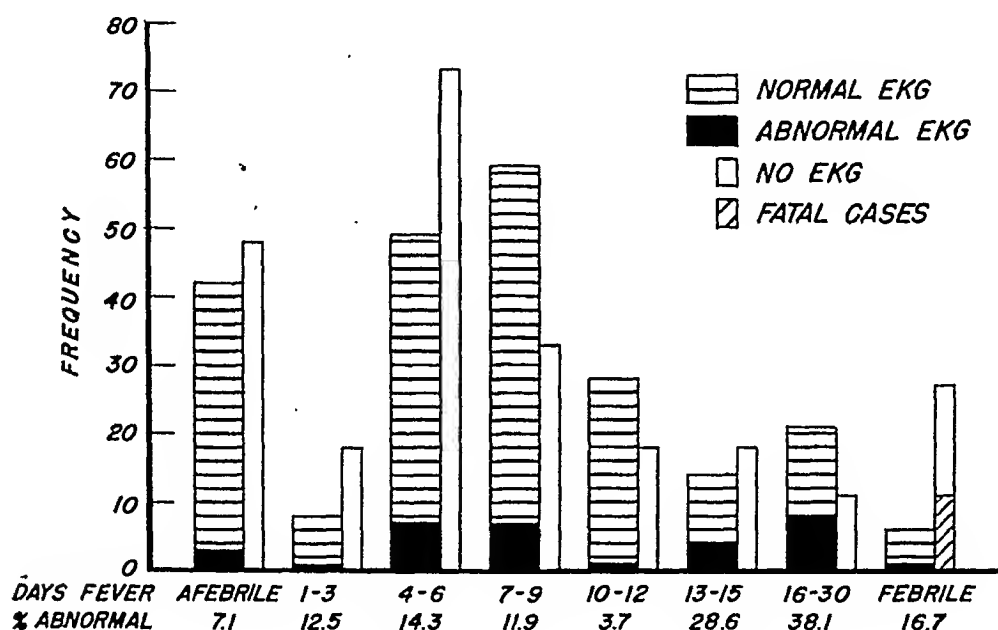


Fig. 6.—Distribution of 226 electrocardiograms in 467 cases of poliomyelitis according to days of fever.

teen patients were febrile for thirteen to fifteen days and 4 (28.6 per cent) showed abnormalities in the electrocardiogram. Twenty-one patients were febrile from sixteen to thirty days; 8 (38.1 per cent) had abnormal tracings. There were 6 patients who were febrile throughout their acute illness and 1 (16.7 per cent) had an abnormal electrocardiogram. The incidence of abnormal tracings rises inconstantly with an increase in the duration of the febrile period. Acute poliomyelitis complicated by intercurrent infection was not considered. The effect of fever per se upon the electrocardiogram was disregarded because temperature elevation influences the heart rate and does not produce the other abnormalities noted. Furthermore, in many instances the abnormalities remained after the patients became afebrile. Since there was a significant correlation between the frequency of abnormal electrocardiograms and the severity of the disease (Fig. 5),

and since the severity of the infection was associated with the duration of the febrile period, a correlation between the frequency of abnormal electrocardiographic patterns and the duration of fever could be expected. One hundred twenty patients were afebrile after seven days of illness; 13 (10.8 per cent) showed abnormal tracings. Of the 79 patients whose febrile period was longer than seven days, 19 (24.1 per cent) had abnormalities in the electrocardiogram.

Day of Initial Electrocardiogram.—The 226 tracings were arranged according to the day of the disease on which the initial electrocardiogram was taken (Fig. 7). By inspection it is evident that the abnormal tracings were scattered over a sixty-day period. The initial tracing was taken within the first two weeks of the disease in 171 cases (75.3 per cent). The lack of significant change in the frequency of electrocardiographic abnormalities as the duration of illness increased

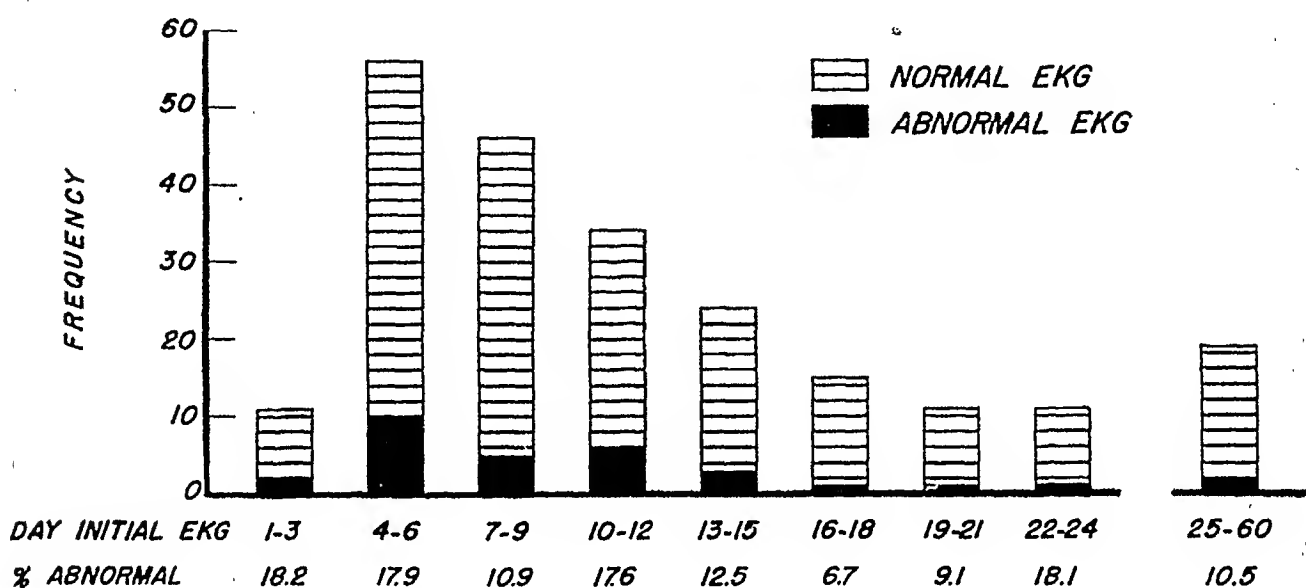


Fig. 7.—Distribution of 226 electrocardiograms in 467 cases of poliomyelitis according to day of initial electrocardiogram.

suggests that (1) the electrocardiographic abnormalities occur early in the disease, (2) they do not increase in frequency as the disease runs its course, and (3) they tend to persist for at least several weeks. The finding of continued changes in repeated tracings mitigates against the possibility of rapid return to normal. This is in agreement with Neubauer⁵ who found that electrocardiographic evidence of myocarditis in diphtheria and other childhood infections (scarlet fever, pertussis, and measles) persisted for at least two to three weeks.

An analysis was made of the electrocardiographic findings in 226 patients (Fig. 8).

Arrhythmias.—Sinus tachycardia, over 140 per minute, and unquestionably disproportionate to the temperature, was observed in 9 cases (4.0 per cent). In 2 cases (0.9 per cent) extrasystoles were recorded, one of auricular and the other of ventricular origin.

P Waves.—The P waves were abnormally high and peaked in 6 cases (2.7 per cent). This was noted in Leads II and III in 4 patients and in Lead II in the 2 remaining patients.

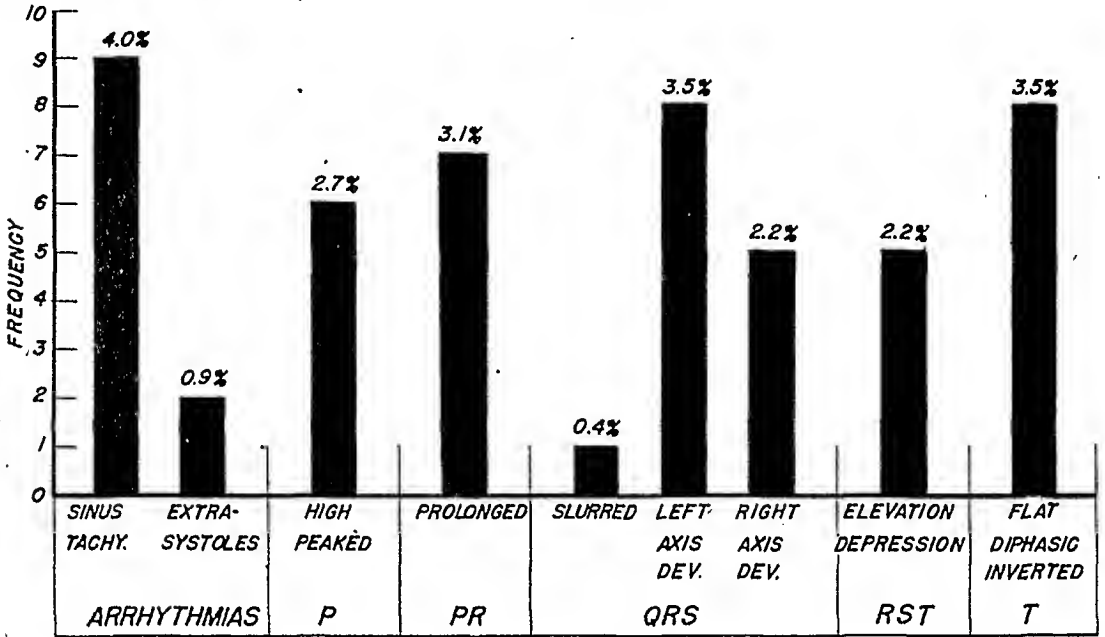


Fig. 8.—Analysis of electrocardiographic observations in 226 cases of poliomyelitis.

P-R Interval.—Abnormal prolongation of the P-R interval beyond that expected for the patient's age and heart rate (according to the scale of Ashman and Hull⁶) occurred in 7 cases (3.1 per cent). The patients ranged in age from 2 to 14 years and the longest P-R interval was 0.22 second (Fig. 9). Subsequent tracings taken from one to three weeks after the initial electrocardiogram showed improvement in 3, no change in 2, return to normal in 1, and progressive lengthening of the P-R interval in 1 case.

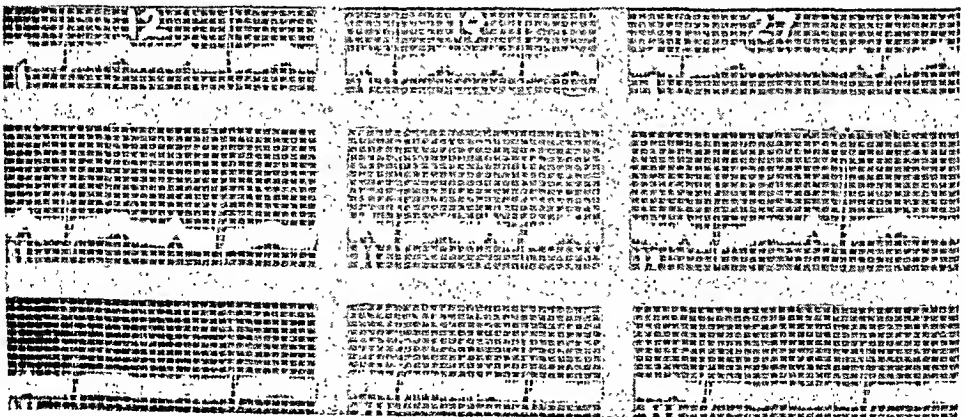


Fig. 9.—Case A-86; 9 years of age; spinal poliomyelitis (grade II severity). Twelfth day: rate, 96; P-R interval, 0.22 second. Nineteenth day: rate, 100; P-R interval, 0.16 second. Twenty-seventh day: rate, 90; P-R interval, 0.15 second.

QRS Complex.—Abnormal slurring of the QRS complex was found in Lead I in 1 case (0.4 per cent). In 8 patients (3.5 per cent) there was an unexplained left axis deviation. Although many patients presented a slight right axis deviation which was considered normal for their age, 5 (2.2 per cent), ranging in age from 10 to 16 years, showed definite right axis deviation in addition to other abnormalities (Fig. 10).

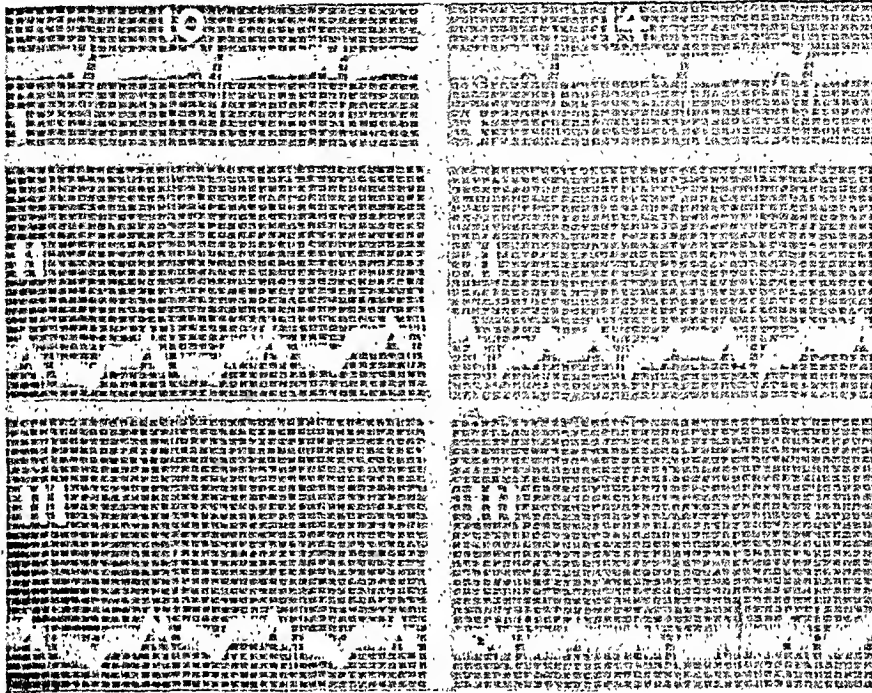


Fig. 10.—Case A-78; 10 years of age; bulbo-spinal poliomyelitis (grade IV severity). Tenth day: rate, 125; P-R interval, 0.14 second; depressed T_1 , T_2 , and T_3 ; S- T_2 and S- T_3 depressed; right axis deviation. Fourteenth day: rate, 120; P-R interval, 0.12 second; flattened T_1 ; T_2 and T_3 upright; S- T_2 and S- T_3 less depressed; right axis deviation less marked.

RS-T Segment.—Abnormal deviation of the RS-T segment from the iso-electric line was noted in 5 cases (2.2 per cent). In 1 case elevation occurred in Leads II, III, and IV F and persisted in four subsequent tracings taken over a period of two months. Another case showed RS-T elevation in Lead IV F; the abnormality was not present in a repeated tracing fifteen days later. There was depression of the RS-T segment in 3 cases. In 1 patient the change occurred in Leads I and II and was not present ten days later. In another the depression was noted in Leads II and III and persisted in a tracing taken eight days later (Fig. 10). In the third patient the depression occurred in Lead I and persisted in four subsequent tracings taken over a period of two months. This is the patient who, in addition to other abnormalities, showed RS-T elevation in Leads II, III, and IV F.

T Waves.—The T waves were flattened, diphasic, or inverted in 8 cases (3.5 per cent). This abnormality occurred in Lead I in 1 case, Leads I and II in 2 cases, Leads I, II, and III in 1 case (Fig. 10), Leads I, II, III, and IV F in 2 cases, Leads I and IV F in 1 case, and in Leads II and III in 1 case. Subsequent tracings were obtained in 7 of the 8 cases, with improvement or exaggeration of the abnormality in 5 and no change in 2 cases.

EVALUATION OF ELEVEN FATAL CASES

Eleven (2.4 per cent) of the 467 patients with acute poliomyelitis succumbed. Unfortunately, tracings were not obtained in these patients because of their grave condition. A clinical analysis of the fatal cases (Table I) reveals that 9 of the 11 patients had poliomyelitis of Grade 4 severity and 2 of Grade 3; all were febrile from the onset of their illness until death; cardiac enlargement was noted in 2 cases, mitral systolic murmurs in 2 cases, and heart rates over 140 per minute in 2 cases; cyanosis was recorded in 10 of the 11 patients. Age, sex, and race were not important factors in this group.

Autopsies were performed on 6 of the 11 patients. The cardiac findings (Table II) consisted of subepicardial petechiae in all 6 cases, dilatation of the right ventricle in 2, dilatation of both ventricles in 1, decreased consistency of the myocardium in 4, and no gross abnormalities in 1 case. Microscopic examination of the heart in 4 cases showed interstitial edema in all 4, congestion in 3, and perivascular and interstitial cellular reaction in 2 cases. Accompanying changes in the lungs in 6 cases (Table III) included congestion in all 6, edema in 4, subpleural hemorrhages in 2, interstitial pneumonitis in 3, patchy atelectasis in 2, terminal aspiration pneumonia in 2, and lymphoid hyperplasia of the bronchial walls in 3 cases.

TABLE I. CLINICAL SUMMARY OF ELEVEN DEATHS FROM POLIOMYELITIS

CASE	AGE	SEX	COLOR	SEVERITY	DAYS OF FEVER	CLINICAL FINDINGS IN HEART			
						MURMURS	TACHYCARDIA	CARDIAC ENLARGEMENT	CYANOSIS
1	7	M	W	IV	Febrile	○	+	○	+
2	10	M	W	IV	Febrile	○	○	○	+
3	8	M	W	IV	Febrile	○	○	○	+
4	9	M	W	IV	Febrile	+	+	○	+
5	9	F	W	IV	Febrile	○	○	○	+
6	14	M	W	IV	Febrile	○	○	○	+
7	8	M	W	III	Febrile	+	○	+	+
8	14	F	W	IV	Febrile	○	○	○	+
9	17	M	W	IV	Febrile	○	○	+	+
10	6	F	W	IV	Febrile	○	○	○	+
11	41	M	W	III	Febrile	○	○	○	Not recorded
Totals						2	2	2	10

TABLE II. PATHOLOGIC FINDINGS IN THE HEART IN FATAL CASES OF POLIOMYELITIS (SIX AUTOPSIES)

CASE	GROSS			MICROSCOPIC		
	SUBEPI-CARDIAL PETECHIAE	VEN-TRICULAR DILATATION	DECREASED CON-SISTENCY MYOCARDIUM	INTER-STITIAL EDEMA	CONGESTION	PERIVASCULAR AND INTERSTITIAL CELLULAR INFILTRATION
1	+	○	+	+	+	○
2	+	Right	+	+	+	+
3		No autopsy				
4	○	○	+	+	+	+
5	+	Right	○	+	○	○
6		No autopsy				
7		No autopsy				
8		No autopsy				
9	+	Right and left	+	No microscopic study		
10	○	○	○	No microscopic study		
11		No autopsy				
Total	4	3	4	4	3	2

TABLE III. PATHOLOGIC FINDINGS IN LUNG IN FATAL CASES OF POLIOMYELITIS (SIX AUTOPSIES)

FINDING IN LUNG	NUMBER OF CASES
Congestion	6
Edema	4
Subpleural hemorrhages	2
Interstitial pneumonitis	3
Patchy atelectasis	2
Aspiration pneumonia	2
Lymphoid hyperplasia of bronchial walls	2

DISCUSSION

The cardiac abnormalities detected clinically in the present study of acute poliomyelitis were insufficient to warrant a diagnosis of myocarditis. According to Neubauer,⁵ however, myocarditis may exist in certain acute infectious diseases even though clinical findings are slight or absent. The mitral and aortic systolic murmurs found are difficult to evaluate inasmuch as they often occurred in

febrile patients and in conjunction with normal tracings. The murmurs in poliomyelitis certainly do not indicate valvular disease, unless the latter pre-existed. Sinus tachycardia, unless persistent, and premature contractions without additional evidence of cardiac involvement do not constitute heart disease, but the presence of either disturbance merits a complete cardiac evaluation. It is obvious that cardiac enlargement or unexplained cyanosis likewise should be investigated fully. One hesitates to interpret the high, peaked P waves as indicative of auricular disease, especially in the absence of notching or widening. The fact that the P-wave abnormalities disappeared in repeated tracings in some patients suggests that their presence might have been due to a toxic effect of the disease. The abnormally prolonged P-R intervals, which changed considerably in most instances, may represent true A-V conduction defects. The slurred QRS complex in Lead I in one patient probably signifies a myocardial abnormality, as the complex was of average amplitude. The finding of left axis deviation in children may possibly be abnormal, although the cause for this condition was obscure. Right axis deviation occurred frequently in young patients but was noted only if there were associated abnormalities. In some of these patients the axis deviation was marked. Significant deviation of the RS-T segment is reasonable evidence of a myocardial disorder. Inversion or flattening of the T wave in Lead I may be interpreted in the same light.

The question of the influence of electrolyte imbalance upon the electrocardiogram arises when one considers that the disease was prevalent in the summer months and the patients were generally treated with hot packs. This possibility is excluded on the basis that the fluid balance of the patients was maintained and sufficient salt supplied. The effects of electrolytic disturbances upon the Q-T interval were not observed in any of the tracings.

The only drugs received by some of the patients which conceivably might have influenced the electrocardiographic pattern were prostigmine and atropine. These drugs were given to all patients with acute poliomyelitis in 1943, to alternate patients in 1944, and to none of the patients in 1945. Prostigmine was used in doses of 10 to 15 mg. and atropine in doses of 0.2 to 0.3 mg. orally three times a day for two weeks. A few patients received 0.5 to 1.0 mg. prostigmine and 0.2 to 0.3 mg. atropine intramuscularly for one week. In only one of the thirty-two patients with abnormal tracings was there a possible time relationship between the use of the drugs and the electrocardiographic abnormalities. The RS-T segment was depressed in Leads I and II in this patient. No other abnormalities could be attributed to the use of medication. Digitalis had not been administered to any of the patients who showed electrocardiographic changes.

If the pathologic findings in the present study may be correlated with the electrocardiographic abnormalities, it is reasonable that a poliomyelitic myocarditis may be suspected by electrocardiogram. As certain of the microscopic changes observed represent toxic, degenerative, or anoxic effects, with or without inflammatory reaction, one may infer only that myocardial derangement exists, particularly since the changes in the electrocardiograms are neither uniform nor specific.

The fatal cases presented little clinical evidence of cardiac disease. The cyanosis of these patients was more likely due to respiratory paralysis than to myocardial involvement. Tracings in these cases might have contributed to a better understanding of myocardial disease in poliomyelitis.

In this study the electrocardiograms were more instructive than were the clinical findings in determining the presence of myocardial derangement. The correlation of electrocardiographic abnormalities with severity of infection and the finding of myocardial changes in a high percentage of fatal cases make a thorough study of the cardiovascular system a necessity in all patients with severe poliomyelitis. Since abnormalities occur early in the disease, tracings should be taken as soon as possible. Serial electrocardiograms showing the progress of the changes are more informative than isolated tracings.

SUMMARY

1. The cardiac status of 467 patients suffering from acute anterior poliomyelitis is reviewed.

2. Electrocardiographic abnormalities appeared in 32 (14.2 per cent) of 226 patients. A significant correlation exists between the frequency of abnormalities and the severity of the disease. Electrocardiographic changes may occur early in this disease and tend to persist for at least several weeks.

3. In all patients in whom abnormalities are detected, serial electrocardiograms are recommended.

4. Autopsies performed in six of eleven fatal cases revealed pathologic changes in the myocardium in all but one instance.

We are indebted to Dr. A. C. LaBocchetta, Chief Resident Physician, Philadelphia Hospital for Contagious Diseases, for valuable suggestions in the preparation of this study.

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Clinical Reports

LUTEMBACHER'S SYNDROME COMPLICATED BY ACUTE BACTERIAL ENDOCARDITIS

REPORT OF A CASE DIAGNOSED DURING LIFE

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THE association of a large interauricular septal defect and mitral stenosis (Lutembacher's syndrome) is relatively rare, and the complication of this combination of lesions by bacterial endocarditis has been clearly described in but one previous case²; a second instance was briefly alluded to by Jacobius and Moore.³ The case herein described therefore seemed worthy of record.

In all probability the occurrence of the Lutembacher syndrome is much less rare than its infrequent clinical recognition would imply, yet the diagnosis can probably be made with reasonable certainty in most cases as the features of the syndrome become more widely known.

CASE REPORT

C. B., a 44-year-old white Canadian spinster and clerical worker in the New Haven Hospital, was first seen in the outpatient clinic in 1934 where she presented herself for a routine employee's examination. She offered no complaints but remarked that she had been known to have had high blood pressure for at least two years, that both parents and two siblings had died of high blood pressure and apoplexy, and that six living siblings also had high blood pressure (all six died within the next decade of either cerebral vascular accidents or congestive heart failure).

The patient had had influenza in 1927, a tonsillectomy in 1923, and no other known illness. She specifically denied rheumatic fever and chorea by name and symptoms, and she did not recall having had many sore throats as the indication for the tonsillectomy. On systemic review of symptoms she acknowledged occasional awareness of irregularity in the beating of the heart, that her ankles were sometimes slightly swollen toward the end of the day, and that exertion evoked dyspnea but that ordinary activities did not cause breathlessness; she denied orthopnea and paroxysmal dyspnea. She had never been cyanotic so far as she was aware.

Examination on this occasion disclosed a well-developed and well-nourished woman with normal coloration. The blood pressure was 220/130 in both arms and slightly higher in the legs. The retinal vessels revealed only minimal sclerotic changes. The heart seemed slightly enlarged, there was an apical systolic shock, and a loud systolic murmur was audible over the entire pre-

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cordium. No signs of congestive failure were detected. Renal function studies gave normal results, and the Kahn test for syphilis was negative. A diagnosis of hypertensive cardiovascular disease was made, and for a few months the patient received at first small and later large doses of potassium thiocyanate (serum concentrations reached 10 to 20 mg. per cent) without convincing influence on the fluctuating blood pressure, which declined as low as 160/105 during control periods as well as during thiocyanate medication. The patient lost interest in the therapeutic efforts and terminated her visits.

Five years later she returned for a few months for the symptomatic treatment of occasional generalized headache associated with vomiting. At this time a systolic thrill over the precordium was noted together with a harsh systolic murmur transmitted to the left infrascapular region, and the apical first sound was described as increased in intensity and rumbling in quality. The electrocardiogram (Fig. 1) showed prolonged A-V conduction, right axis shift, abnormally tall,

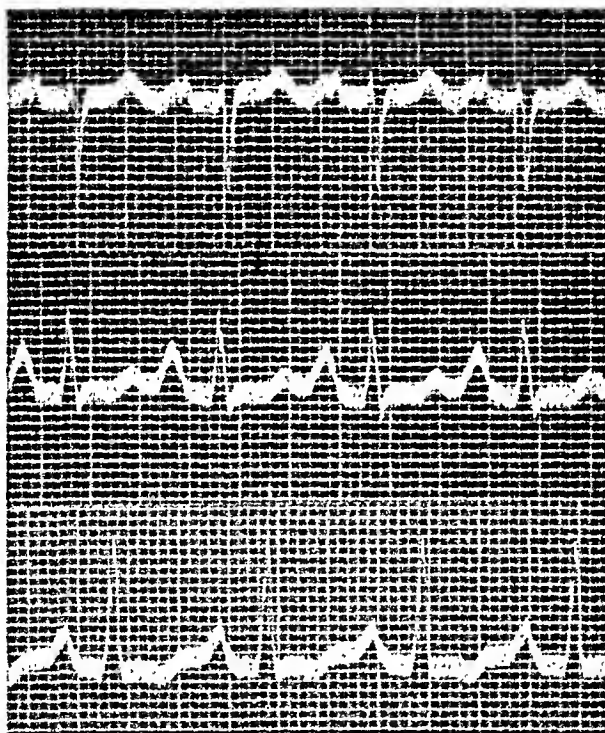


Fig. 1.—Electrocardiogram made in 1939. The tracing shows long P-R intervals, slurred QRS complex, tall notched P waves, and right axis deviation.

broad, and notched P waves, and slurring of QRS complexes. The question of a congenital anomaly was raised for the first time. Roentgenographic study of the heart (Fig. 2) disclosed marked enlargement of the left ventricle as well as marked prominence of the pulmonary conus and arteries, and a diagnosis of a patent ductus arteriosus and interventricular septal defect was ventured. Contact with the patient was again lost for three years.

In January, 1943, the patient was admitted to the New Haven Hospital for an acute respiratory illness which proved to be lobar pneumonia of the right upper and middle lobes, and pneumococcus type III was recovered from the sputum and the blood. On this occasion there was moderate cyanosis of the lips and nail beds, and ectopic ventricular beats were detected. She was treated with digitalis and sulfamerazine, the temperature fell to normal within three days, the cyanosis promptly disappeared, and a complete recovery was made. The blood pressure ranged from 200/114 to 130/80 during hospitalization. The arm-to-tongue circulation time (with decholin sodium) was twenty seconds and the venous pressure (direct method) was 6.5 cm. of water; these observations were made after digitalization.



Fig. 2.—X-ray films made in 1939. There is enlargement of the left ventricle and prominence of the pulmonary conus and arteries.

The patient was discharged on the eleventh day following admission. She discontinued the digitalis a month later and maintained her usual satisfactory state of health until December, 1944, when fatigue became a conspicuous symptom. She consulted a physician who discovered râles at the right apex and demonstrated pulmonary infiltration on the right side by roentgenographic examination (Fig. 3). She was advised to stop work and was placed at bed rest. She did not improve, and in February, 1945, she developed severe pain low in the back; lesser pains involved the right knee and shoulder, but the joints were not swollen, hot, or reddened. Presently anorexia and night sweats appeared, but she was unaware of fever. On a few occasions red spots were noted on the trunk, but the patient recalled no soreness of the fingers. She re-entered the hospital on March 8, 1945. Her age at this time was 55 years.

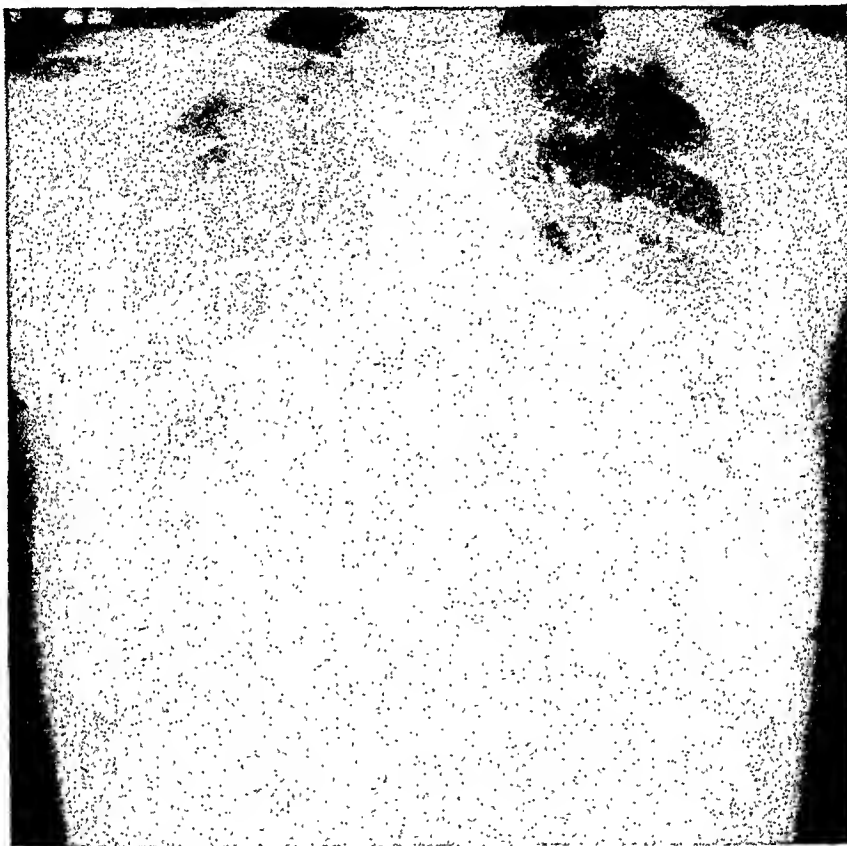


Fig. 3.—X-ray film made in January, 1943. In addition to the findings noted in 1939, there is now pulmonary infiltration on the right side.

On admission for this last hospitalization, the patient was acutely ill, weak, and perspiring but not cyanotic. Her speech was slow and thick. Rectal temperature was 101.5° F. The blood pressure ranged between 120/84 and 116/78. The upper half of the right lung field and the lower half of the left revealed dullness and moist râles in abundance. The cardiac signs recorded were as follows: evidence of a huge heart (a diffuse apex impulse was apparent in the fifth and sixth left intercostal spaces in the region of the apex, and the impulse was visible in the mid-axillary and posterior axillary lines), a fundamentally regular rhythm with frequent ectopic ventricular beats, a loud and harsh systolic murmur audible all over the precordium, and a low-pitched rumble in the latter half of diastole with presystolic accentuation in the region of the apex; the apical first sound was loud and sharp, and the pulmonic second sound was abnormal in that it exceeded the aortic second sound in intensity. A presystolic precordial thrill was described by several observers. The liver was moderately enlarged, there were signs suggestive of ascites, and marked tenderness was present in both costovertebral angles. There was no peripheral edema, and the fingers were not clubbed. Two red spots suggesting petechiae were noted on the lower

eyelids, and one small hemorrhage was seen in the right retina. The red blood cell count was 5.56 millions per cubic millimeter and the hemoglobin was 14 grams. The white cells numbered 25,600 per cubic millimeter, of which 68 per cent were polymorphonuclear cells. The corrected erythrocyte sedimentation rate was 22 mm. per hour (Wintrobe method). The urine specific gravity was 1.023, albumin was Grade 2, and the centrifuged sediment contained a moderate number of white cells as well as hyaline and granular casts. The blood nonprotein nitrogen was 95 mg. per cent. Venous pressure was 14.5 cm. of water, and the circulation time from arm to tongue was 23 seconds. The electrocardiogram (Fig. 4) disclosed sinus rhythm with prolonged A-V conduction time, abnormally broad and notched P waves, frequent ectopic ventricular beats, right axis shift, abnormal slurring of the QRS complexes in the limb leads, and T waves that were abnormal in being flat in Lead I.

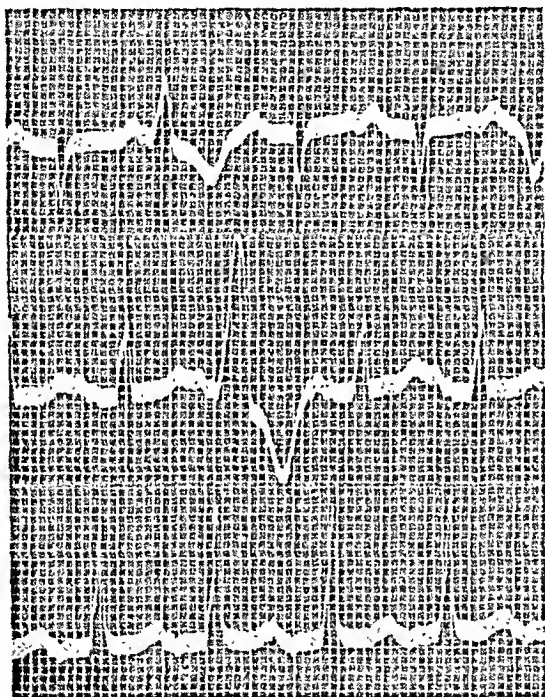


Fig. 4.—Electrocardiogram made in March, 1945. The principle findings are long P-R intervals, frequent ectopic ventricular beats, right axis shift, slurring of the QRS complexes, and flat T waves in Lead I.

The course in the hospital was brief and dramatic. Because of evidence of heart failure, the patient was rapidly digitalized with 4 units of digifolin given parenterally. The persistence of blood pressure at an unusually low level for the patient and the development of oliguria led to the transfusion of 500 c.c. of blood and the slow intravenous injection of 1,500 c.c. of 5 per cent glucose solution, but no apparent benefit ensued. A culture of the blood, taken on admission, revealed pneumococcus type V at the end of forty-eight hours, confirming a prior suspicion of bacterial endocarditis. Treatment with penicillin was promptly instituted; 50,000 units were given intravenously at once, and a slow intravenous infusion of 300,000 units per day was continued. However, that evening there appeared a livid discoloration of the face which by the next morning had become purple and had spread to the neck and shoulders (Fig. 5). The blood pressure continued to decline slowly in spite of another transfusion of blood, the extremities became cold and mottled, respirations grew gradually more labored, coma ensued, and the patient died in the afternoon of the fourth hospital day.

The final clinical diagnosis was acute bacterial endocarditis complicating a congenital cardiac anomaly consisting of a large interauricular septal defect with associated mitral stenosis (Lutembacher syndrome). The pulmonary lesions were suspected to be infarcts, and the renal pathology was attributed to the bacterial endocarditis with either embolic or toxic injury.



Fig. 5.—Showing the hemorrhage into the skin of the face and shoulders.

Diagnostic Discussion.—Each of the authors independently interpreted the cardiac abnormality before death as Lutembacher's syndrome. The diagnosis was made with complete conviction on the basis of the following arguments:

1. The loud, harsh, widely radiating precordial *systolic* murmur and thrill, first noted in 1940, was considered referable to the markedly increased blood flow through the greatly enlarged pulmonary artery which was known to be present from previous roentgen examinations. Only a few lesions could yield these signs: an arteriovenous fistula between the aorta and pulmonary artery, an aneurysm of the pulmonary artery, or a large auricular septal defect with considerable shunting of blood from the left auricle to the right. The last seemed the most acceptable in view of the electrocardiographic features discussed below. The additional presence of mitral stenosis seemed established by the classical physical signs of that lesion: shocklike apical first sound, low-pitched apical diastolic murmur with presystolic accentuation, and apical diastolic thrill noted in the last illness.

2. The electrocardiographic features of marked right axis shift (in spite of considerable hypertension in the past), and the tall, broad, and notched P waves (implying auricular hypertrophy; right, rather than left, for the lateral roentgeno-

gram showed no enlargement of the left auricle) seemed entirely logical developments of a large left-to-right auricular shunt, causing overloading of the right auricular and right ventricular chambers with sufficient hypertrophy of the latter to overbalance the effects of the chronic hypertension on the electrocardiographic axis. The long P-R interval could be attributed either entirely or in part to abnormally long conduction time within the enlarged right auricle or to a large interauricular septal defect located sufficiently low to affect the A-V node.

3. The extraordinarily prominent pulmonary artery and branches in the roentgenogram of the chest was considered typical of interauricular septal defect with a large shunt. Pulmonary artery enlargement of this unusual degree is not, in our experience, seen with patent ductus arteriosus (the previous roentgen diagnosis) and was regarded as a highly unlikely expression of mitral stenosis alone, particularly in view of the absence of enlargement of the left auricle. A large aortic-pulmonary artery fistula seemed excluded by the absence of a wide pulse pressure and by the long course without heart failure; moreover, neither this lesion nor aneurysm of the pulmonary artery could account for the abnormal auricular electrocardiogram.

4. Although primary chronic rheumatic myocarditis and high-grade mitral stenosis and insufficiency could also explain the electrocardiographic abnormalities, roentgenographic study failed to show the expected enlargement of the left auricle. Moreover, mitral stenosis of such extreme degree as to result in the enormous cardiac enlargement would probably have led to congestive failure long before the terminal illness. That "incidental" mitral stenosis could, nevertheless, be present without left auricular enlargement seemed acceptable on the basis of an auricular septal defect sufficiently large to receive a considerable part of the left auricular blood, thereby avoiding strain of the left auricle.

The diagnosis of the Lutembacher syndrome was thus made clinically.

Necropsy Findings.*—The heart weighed 695 grams. In situ, it was seen that almost the entire anterior surface of the heart was composed of right auricle and right ventricle. The pulmonary conus was extremely large. On opening the right auricle a large circular defect measuring 3.0 cm. in diameter involved the anterior superior part of the septum (Fig. 6). The valve measurements were as follows: tricuspid, 14 cm.; pulmonic, 9.5 cm.; mitral, 7 cm.; and aortic, 6.5 cm. The right ventricle was 8 mm. thick and the left ventricle 12 mm. thick. The right auricle and ventricle were tremendously dilated. The mitral valve showed thickening and rolling of the free edges with marked thickening and fusion of the chorda tendineae. Engrafted on the right leaflet of the mitral valve was a large, red, friable, and fungating thrombus which extended outward and partially blocked the mitral orifice (Figs. 6 and 7). The free edge of the tricuspid valve was edematous. The cusps of the aortic valve showed a very slight degree of fusion at the commissures. The pulmonary valve was not remarkable. A microscopic section of the mitral valve revealed an acute process with necrotic polymorphonuclear leucocytes and a vegetation made up of clumped fibrin, acute inflammatory cells, and clumps of gram-positive cocci.

There were numerous small, red, wedge-shaped infarcts in the right lung. Both lungs showed small areas of focal pneumonia. There was a septic infarct in the spleen. A section of skin from the area of livid cyanosis revealed a great deal of hemorrhage below the epithelium, and there was a marked acute arteritis with necrosis of some of the artery walls, while other arteries were plugged with small hyaline thrombi. The other organs were not remarkable.

*The autopsy was performed by Dr. Herbert Axilrod, Department of Pathology, Yale University School of Medicine.

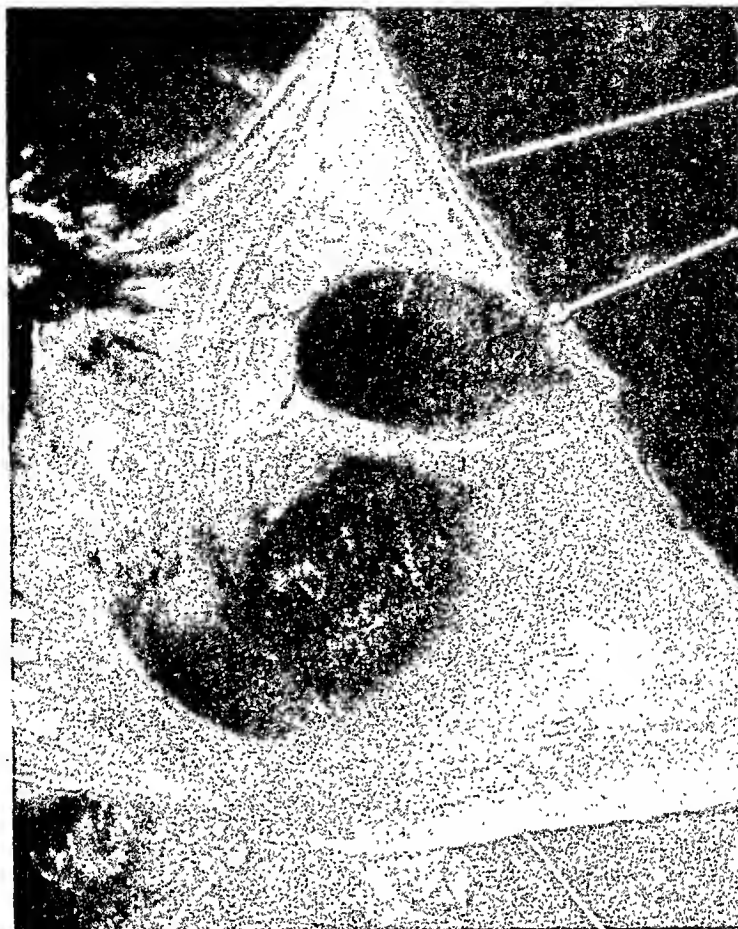


Fig. 6.—Showing the opened left auricle disclosing the large defect in the auricular septum and the vegetation on the mitral valve.



Fig. 7.—Showing a close-up view of the massive vegetation on the mitral valve.

COMMENTS

It was noted that the patient was not ordinarily cyanotic, which is consistent with the arteriovenous direction of the blood flow that prevails with interauricular septal defects. The cyanosis that appeared late in the terminal illness implies that a reversal of the shunt to a veno-arterial direction had developed, and this would be a logical result of ultimate dilatation and failure of the chronically overstrained right ventricle. Moreover, lesions of the lung, such as infarcts seen at necropsy, could have contributed to the cyanosis. The intense and livid cyanosis that spread over the face, neck, and upper thorax during the last twelve hours of life seems to have been due to bleeding from arterioles in the skin; similar livid cyanosis has been mentioned as a terminal event in other cases of Lutembacher's syndrome without comment as to vascular lesions in the skin or association with bacterial endocarditis.¹

It is regrettable, in retrospect, that the early suspicion of bacterial endocarditis did not lead to the prompt institution of penicillin therapy, for when the diagnosis was proved by blood culture, the loss of forty-eight hours' time in the presence of an acute pneumococcal infection probably accounted for the therapeutic failure. Success in the treatment of *acute* bacterial endocarditis demands institution of penicillin therapy at the earliest suspicion of the diagnosis without waiting for the results of blood cultures.

When the diagnosis of acute bacterial endocarditis became established, the pulmonary lesions were attributed to embolism in the pulmonary circulation; the urinary abnormalities and the conjunctival and retinal hemorrhages were viewed as due to emboli in the systemic circulation. The presence of vegetations in close relation to the septal defect or on the adjacent aortic cusp of the mitral valve is ideal for the discharge of emboli into both circulations for, on the one hand, significant volume of blood flows from the higher-placed left auricle into the right side of the heart and pulmonary arteries and, on the other hand, emboli from mitral vegetations would readily enter the left ventricle and systemic arteries. Since at necropsy there were no vegetations near the septal defect, it is presumed that emboli reached the left auricle from mitral regurgitation and that from the left auricle they were swept into the right auricle and the pulmonary circulation.

Survival into the sixth decade is unusual for patients with Lutembacher's syndrome; only four of the twenty-four patients reported on by McGinn and White¹ lived beyond the age of 50 years. Had bacterial endocarditis not supervened, the patient might well have lived considerably longer, for no significant degree of heart failure had developed prior to the terminal illness.

The anatomic characteristics of a rheumatic etiology for the mitral stenosis support those who contend that the mitral lesion is an acquired rather than a congenital accompaniment of the auricular septal defect in Lutembacher's syndrome.

SUMMARY

A case of auricular septal defect with associated mitral stenosis (Lutembacher's syndrome) complicated by bacterial endocarditis is described.

The diagnosis of Lutembacher's syndrome was made clinically and confirmed at necropsy. The diagnostic features are discussed.

The mitral stenosis proved to be of rheumatic etiology.

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THE TETRALOGY OF FALLOT

AN ACCOUNT OF A PATIENT WITH THIS CONDITION SURVIVING OVER FORTY-FIVE YEARS

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THE remarkable combination of congenital cardiac anomalies termed the tetralogy of Fallot presupposes serious circulatory handicaps from early fetal existence. Hence, Abbott's figure¹ of an average life span of 12 years and 9 months for such subjects is not surprising. The survival of subjects with the tetralogy of Fallot to midlife is worthy of note. White and Sprague² record an isolated instance of survival to the sixtieth year. Strandell's patient³ lived fifty-six years and three months, and that of Volini and Flaxman⁴ lived forty-one years. The last two cited subjects died of causes other than their congenital cardiac lesions. The patient herein considered pursued a useful career as an electrical engineer and succumbed to congestive failure at the age of 45 years and 4 months.

Although the patient had been a blue baby, the congenital lesion was not recognized until the third year of life. In the interval between his matriculation at the University of Wisconsin in 1919 and his death in 1945, repeated observations were made. The physical limitations imposed on him by dyspnea, cardiac consciousness, and fatigability were met by an indomitable will and such adjustments as reconciled the task at hand to his cardiac reserve. A responsible position was attained in his professional field. Because of recurrent episodes of tonsillitis, tonsillectomy was performed in 1922. Cholecystectomy became imperative in 1925. Both surgical procedures were well withstood. In 1935 a cerebral vascular accident was manifested by dysarthria, left hemiplegia, and hemiparesthesia. Within ten days, only minor residua of the neurological lesion (slight ptosis of the left upper lid, flattening of the left nasolabial fold, and questionable weakness of the grip in the left hand) could be demonstrated.

The terminal decline was initiated by an upper respiratory infection in November, 1944. Dependent edema advanced from the feet to the legs and to the thighs and the flanks in turn. After a short remission under therapy and rest in the hospital, dyspnea and edema advanced apace. His physical status on the last admittance to the State of Wisconsin General Hospital may be summarized thus: Pronounced cyanosis of the lips, ears, and fingers, obvious dyspnea, gross clubbing of the fingers and toes, extreme engorgement of the veins of the neck, marked edema of the left arm, legs, and trunk up to the flanks, systolic thrill over the left subclavian artery, fine crackling and medium moist râles at both bases, and a palpable liver 3 cm. below the costal margin. The cardiac findings included a diffuse wavy impulse over the entire precordium with accentuation in both second intercostal spaces, systolic thrill in the right second intercostal space, and double thrill in the left second intercostal space. The cardiac borders were percussed as shown in Table I.

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TABLE I

RIGHT (MM.)	INTERCOSTAL SPACE	LEFT (MM.)
45	II	60
60	III	140
72	IV	150
	V	Axilla
	VI	Axilla

Systolic murmurs were heard over the entire precordium. The basal systolic murmur was coarser in quality and was transmitted from the point of maximum intensity in the second left intercostal space to the neck. A diastolic element of this murmur was audible in the second and third left intercostal spaces. A second systolic murmur was heard best in the fourth and fifth left intercostal spaces close to the sternum and was transmitted for considerable distances toward both axillae.

Over a period of fifteen years, evidence of progressive myocardial change had been manifested in electrocardiograms. Initial prolongation of the auriculoventricular conduction (0.24 second) had advanced to 0.32 second without comparable intraventricular delay (0.08 to 0.09 second). The earliest available blood count (May 6, 1920) revealed a polycythemia (hemoglobin, 128 per cent; erythrocytes, 7,010,000 per cubic millimeter). Although fluctuations occurred, the erythrocytosis persisted throughout life (Nov. 23, 1945, hemoglobin, 19.6 Gm. per 100 c.c., or 117 per cent; erythrocytes, 5,160,000; hematocrit readings, 62 and 61 per cent).

The usual supportive measures were supplemented by venesection and the administration of oxygen during the period of the terminal illness. The compensatory order of the polycythemia was appreciated, but it was hoped that temporary improvement through a lessening of the total cardiac load and a decrease in the viscosity of the blood might be accomplished by venesection. The attempt was technically inadequate, so that no conclusion could be derived. Oxygen gave remarkable subjective and objective relief. Sleep was afforded by this means when sedatives alone had become ineffective.

In spite of all therapeutic efforts, the patient's condition after the last admission became steadily worse, and he died Dec. 6, 1945.

Autopsy Findings.—The external appearance has been described in the clinical notes. The heart weighed 790 grams. The aortic and pulmonic orifices were preserved unopened. The mitral orifice measured 12 cm. in circumference; the tricuspid, 15 centimeters. The right ventricular wall was from 0.3 to 1 cm. thick; the left, from 0.9 to 1.1 centimeters. The epicardium was smooth and glistening, but on the serous surface of the right auricular appendage there were several pale irregular, flat, raised areas up to 3 mm. in diameter. The myocardium was gray-pink and firm, and slight scarring was visible grossly.

A defect 3 cm. in diameter was found in the extreme upper part of the interventricular septum. The margins of this defect were smooth and rounded (Fig. 1). The aortic valvular orifice was 3.5 cm. in diameter. There was thickening and stiffening of the valve cusps, which were adherent to one another at the commissures. The aortic orifice was placed almost squarely above the septal defect, being only slightly more to the left than to the right.

The pulmonic valve was bicuspid, and adhesions between the two cusps had converted the valve into a funnel-like structure with the apex pointing distally. The diameter of the valve orifice was thus reduced to 1 cm. (Fig. 2). The cusps were thickened as well as adherent. The pulmonary artery itself was slightly narrowed.

There was localized thickening of the mitral valve along its line of closure, but this did not appear to be severe or extensive enough to impair the function of the valve materially.

Other lesions were chronic passive congestion of the organs in general; hypostatic hemorrhagic bronchopneumonia; central cirrhosis of the liver; old cholecystectomy; arteriosclerotic scarring of the kidneys; one recent renal infarct; subacute interstitial pancreatitis.



Fig. 1.—Septal defect.



Fig. 2.—Pulmonic valve.

The findings in this patient, therefore, fulfilled the anatomic criteria of the classical tetralogy of Fallot. The additional clinical observation of pulmonic regurgitation was explained by the rigidity and incompetency of the bicuspid pulmonic valve.

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CARDIAC ASYSTOLE IN A NORMAL YOUNG MAN FOLLOWING PHYSICAL EFFORT

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THIS is the report of a cardiac asystole of nineteen seconds which occurred in a normal young soldier during a syncopal attack induced by physiologic means. Bradycardia during syncope is a common observation, and very low heart rates have been observed during syncopal attacks induced by various causes.¹⁻¹¹ However, prolonged asystole during syncope is uncommon except in subjects with certain types of heart diseases or with carotid sinus sensitivity. In the present case syncope and asystole occurred while the subject was in the erect posture following a bout of hard physical work. Severe physical exertion has been shown to be frequently followed by an orthostatic hypotension¹²⁻¹⁵ which may be so severe that syncope results.

The Harvard Pack Test¹⁶ was used as the exercise procedure. The subject, stripped to shorts, socks, and shoes, and carrying a pack weighing one-third of his body weight, steps up and down on a platform sixteen inches high once every two seconds for five minutes. This work rate is of such severity that approximately one-third of normal young men fail to complete the required five minutes of effort. On stopping work, the subject sits down and, at intervals over the ensuing five minutes, the heart rate is counted. From these a fitness score is determined.

Following the five-minute sitting period, the subject in this study was placed on a tilt table which was used to change his posture alternately from 70 degrees erect to supine. While erect, the body weight was supported by the legs and no measures were taken to prevent postural sway, other than admonitions to stand still. Except when the erect periods were shortened by syncope, each position was maintained for five minutes during which the heart rate, blood pressure, respiratory rate, and electrocardiogram were repeatedly determined.

CASE REPORT

A white man, 22 years of age, weighing 165 pounds, and 5 feet, 8 inches in height, had completed basic training and for the preceding four months had engaged largely in clerical duties.

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Though somewhat overweight, his performance on fitness tests indicated an average physical fitness. The heart was not examined in detail but was assumed to be normal on the basis of good heart sounds without murmurs, a normal electrocardiogram, and the fact that he had passed several medical examinations without incident and had performed the physical tasks of military basic training without difficulty.

On Oct. 19, 1942, he performed the Harvard Pack Test, became exhausted after four minutes and ten seconds, and developed orthostatic hypotension with syncope in the postexertional standing periods. On Oct. 29, 1942, he performed the test for the second time. He had had a mild common cold for four days but felt quite well. After two minutes and thirty seconds of effort, he was stopped because he began to lag behind the required pace of one step-up per two seconds.

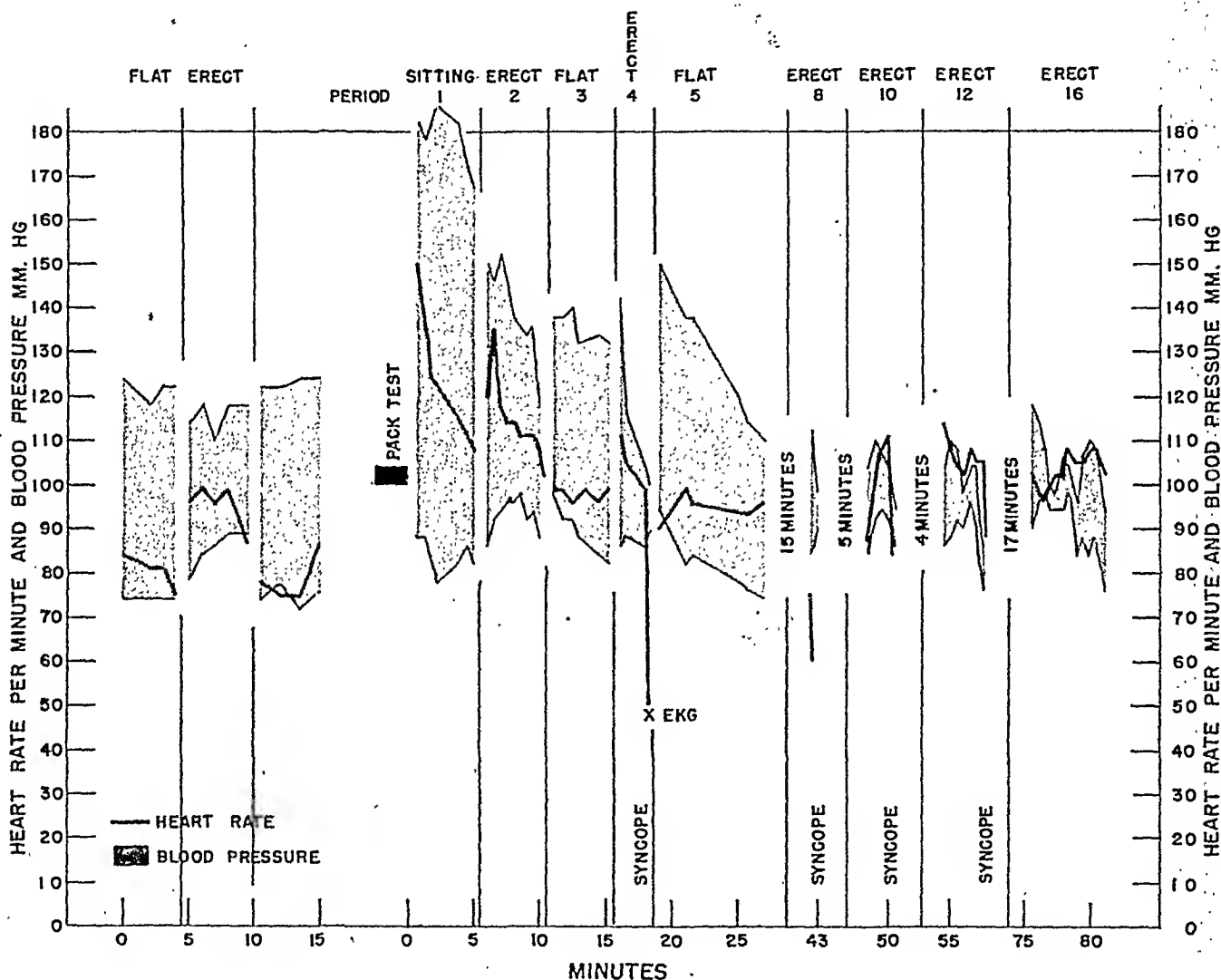


Fig. 1.—Response of blood pressure and heart rate to change of posture before and after severe physical effort (Harvard Pack Test). Heavy dark line, heart rate; shaded area, blood pressure. After Period 5, only the erect periods are plotted. Each of these was preceded and followed by a supine period in which the blood pressure and heart rate were similar to those at the end of Period 5.

Some of the circulatory changes induced by this second test are shown in Fig. 1. The elevated systolic blood pressure and rapid heart rate immediately after exercise (Period 1) are the usual results of physical work. Both the elevated blood pressure and heart rate subsided toward control values during the first erect period (Period 2) which was maintained for the required five minutes without discomfort. The breathlessness and distressing symptoms induced by the work had already disappeared. During the second erect period (Period 4) the systolic blood pressure

LEAD I

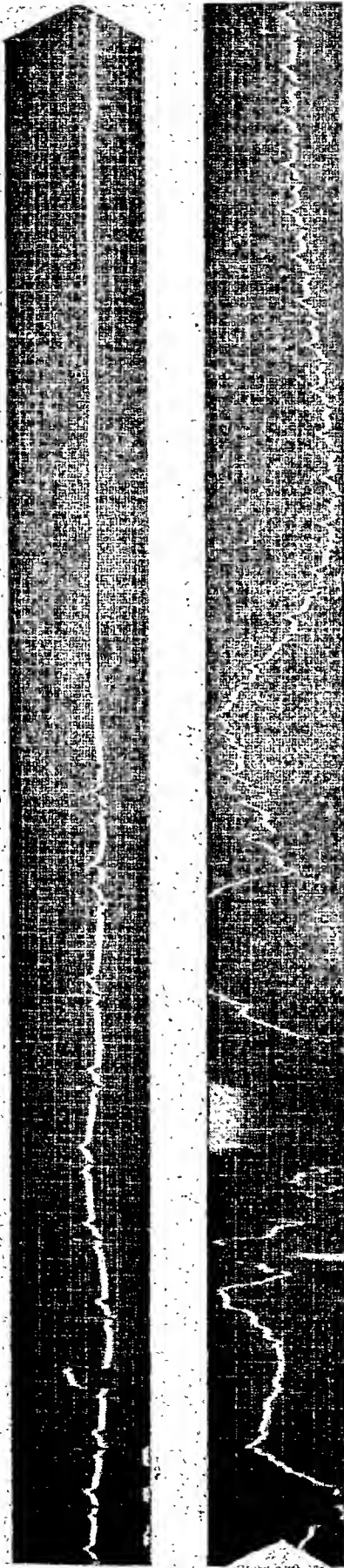


Fig. 2.—Electrocardiogram (Lead I) taken in the erect posture eighteen minutes after stopping work and at the time of collapse. The two strips form a continuous tracing; the lower one follows the upper one without a break in time. The apparent "wavy" following the T wave of the next to the last complex in the upper strip is unexplained.

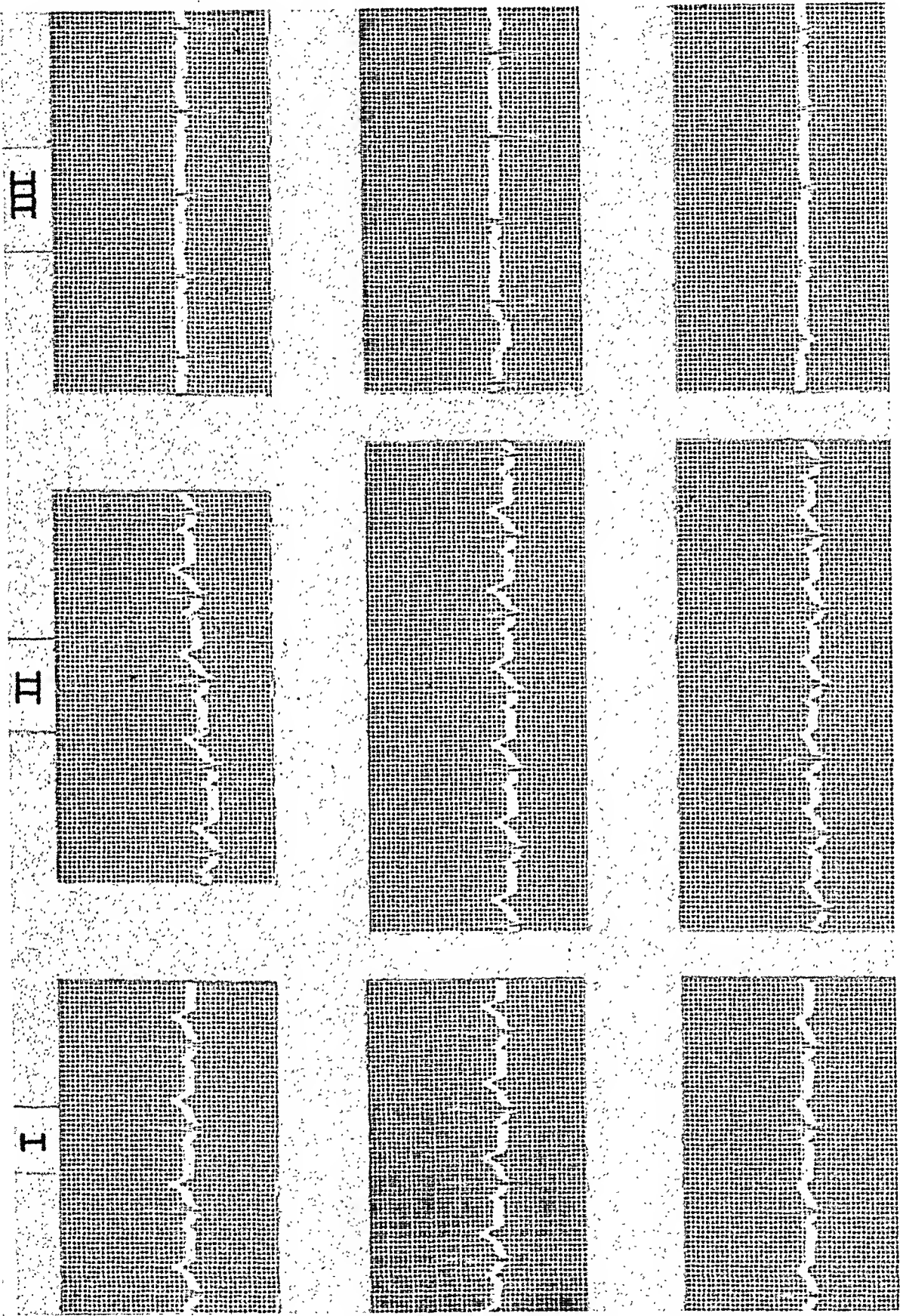


Fig. 3.—Control electrocardiograms before physical exertion. Upper tracings, subject supine; blood pressure, 122/74; heart rate, 87. Middle tracings, subject sitting; heart rate, 94. Lower tracings, subject erect; blood pressure, 118/88; heart rate, 100.

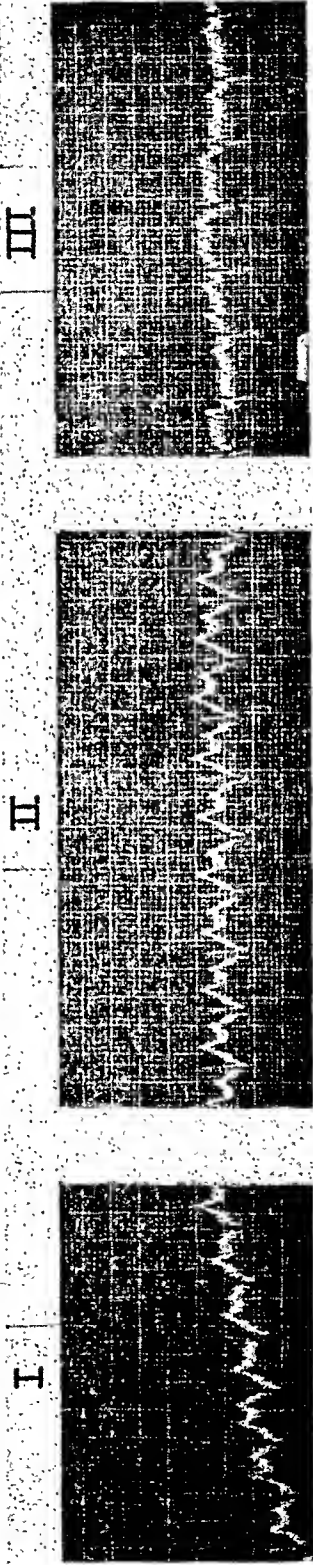


Fig. 4.—Electrocardiogram immediately after cessation of exercise. Subject seated; blood pressure, 182/88; heart rate, 150.

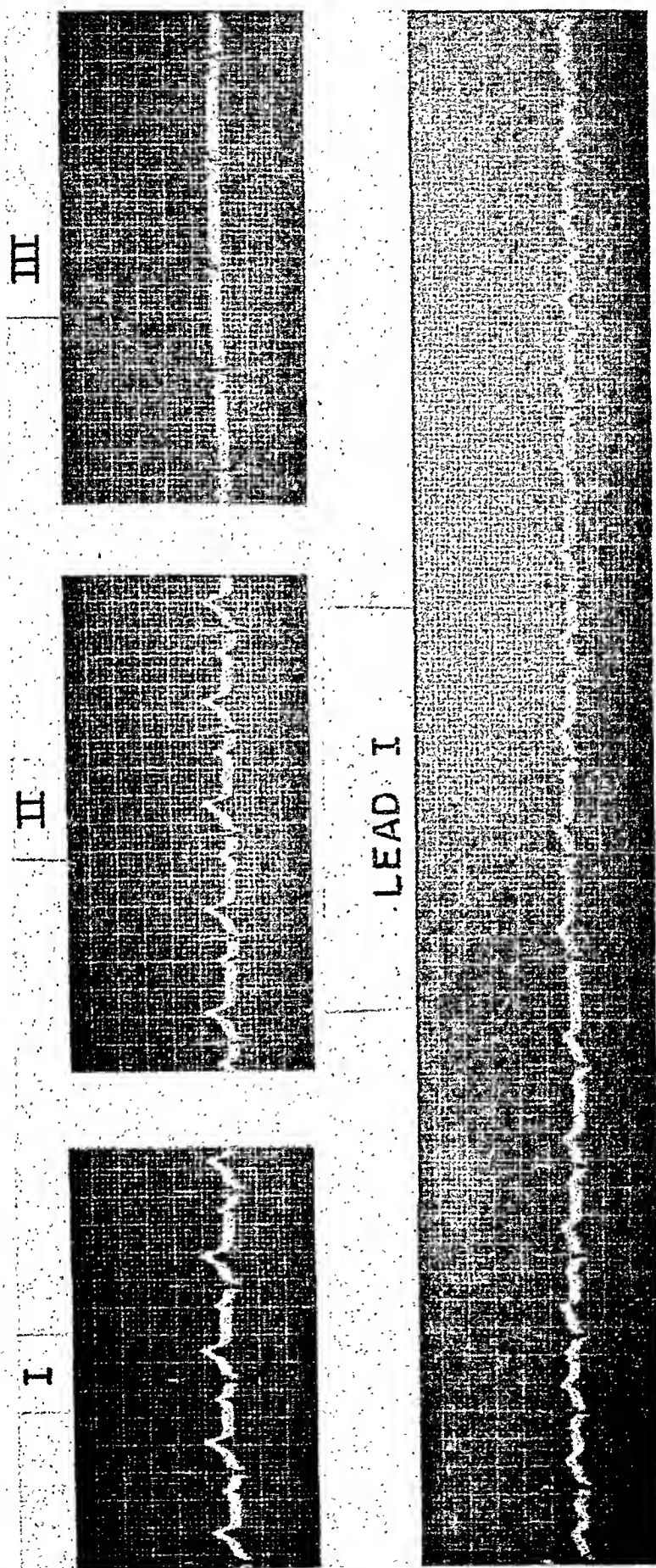


Fig. 5.—Upper tracing, electrocardiogram taken forty-five minutes after exertion. Subject supine, blood pressure, 108/76; heart rate, 90. Lower tracing, electrocardiogram (Lead I) taken in erect posture fifty-six minutes after exertion. Blood pressure, 100/92; heart rate, 105. Note transitory sinus slowing of cardiac rate in the middle of the tracing.

fell steadily, the diastolic blood pressure remained unchanged, and the pulse pressure narrowed markedly. The heart rate, instead of accelerating, slowed progressively. Signs of increasing discomfort and incipient syncope developed. After standing for two minutes and forty-five seconds of this period, the blood pressure was 100/90 and the heart rate, 99 per minute; the subject was in severe distress. Suddenly the heart rate slowed markedly and before the subject could be tilted flat, he lost consciousness, collapsed, and had a short clonic convulsion. After becoming supine, consciousness rapidly returned and, with it, apparently complete subjective recovery.

At the time of the collapse an electrocardiogram was being taken and is shown in Fig. 2. The two strips of this tracing are both Lead I and form a continuous record; the lower strip follows the upper one without a break in time. The tracing shows an increasing sinus bradycardia which leads to complete cardiac standstill. After 10.12 seconds of asystole (beginning of lower strip), the tracing is distorted by the muscular activity of the collapse and convulsion. A little over nineteen seconds (19.08) elapse between the onset of asystole and the first identifiable cardiac complex. This complex has a T wave of markedly increased amplitude which in subsequent complexes quickly reverts almost, but not quite, to the height of the pre-exercise control.

For comparison, pre-exercise control electrocardiograms in the supine, sitting, and 70 degree erect posture are shown (Fig. 3), as well as the tracing taken immediately (from thirty seconds to ninety seconds) after the cessation of work (Fig. 4).

Fig. 1 also shows that the postexertional orthostatic hypotension, syncope, and terminal bradycardia persisted for a considerable length of time. Syncope still occurred when the subject was upright, forty-three minutes (Period 8), fifty-one minutes (Period 10), and fifty-eight minutes (Period 12) after exertion. However, these periods showed a progressive improvement in the circulatory response to the erect posture. With each succeeding period the blood pressure was sustained for a progressively longer time before it suddenly fell and was accompanied by syncope and slowing of the heart rate. It was not until one hour and fifteen minutes after the cessation of exertion (Period 16) that the erect posture could be maintained for the required five minutes, and even then the circulatory response had not yet returned to normal. The widely fluctuating, often low, blood pressure and the markedly narrowed pulse pressure indicated a persisting circulatory instability.

Two electrocardiograms taken during this recovery period are shown in Fig. 5. The upper tracing, taken forty-five minutes after exertion and with the subject supine, is now similar to the pre-exercise control electrocardiogram. The lower tracing is Lead I taken fifty-six minutes after stopping work. The subject was erect; blood pressure, 100/92; pulse rate, 105 per minute. The transitory sinus slowing of the cardiac rate which appears in the middle of the tracing indicates that the conditions which produced the earlier asystole still persisted but to a very much milder degree.

DISCUSSION

The postexertional syncopal attack here described follows the pattern of vasovagal syncope described by Lewis.¹⁷ The sudden cardiac slowing is generally attributed to vagal activity induced in turn by cerebral hypoxia. It has been demonstrated that marked vagal slowing of the heart occurs when the oxygen tension of the blood flowing to the brain is critically lowered^{18,19} or when the volume of the blood flow to the brain is markedly reduced.^{19,20} In the case here described the train of events is believed to have been as follows: hypotension produced deficient cerebral blood flow which resulted in cerebral hypoxia; the latter induced vagal stimulation of sufficient intensity to produce cardiac arrest.

The occurrence of asystole following physical exertion is reported largely because of its intrinsic interest. Here is a complete cardiac arrest induced by physiologic means. One speculates whether this episode may not have greater significance. Sudden death during or after exertion has been repeatedly encoun-

tered, even in apparently healthy young adults and athletes. Such deaths are usually attributed to a pathologic cardiac accident, generally coronary occlusion with myocardial infarction and terminal ventricular fibrillation. Where autopsy has been performed in such deaths, the overwhelming majority have revealed longstanding organic cardiac disease, often of a severe degree.²¹⁻²³ Occasionally no cardiac lesions are found. In both instances, *fresh* lesions capable of producing and explaining the immediate and sudden death are usually absent. This led Weiss²⁴ to call attention to the possibility that sudden death of this type might be the result not of an organic cardiac lesion but of purely circulatory changes, a "physiologic" death. He suggested a fatal vasovagal syncope. The present case demonstrates that cardiac arrest, presumably of vagal origin, can occur under certain circumstances following severe exertion and suggests that this phenomenon may persist for a considerable time after the cessation of effort. In a healthy youth, presumably with a good myocardium and coronary circulation, the heart and the subject recovered from the vagal arrest without apparent ill effect. Perhaps a heart involved by myocardial or coronary artery disease may not recover and death may ensue. Weiss has suggested that diseased hearts are more prone to reflex cardiac stimulation than normal hearts.

In the present case it is possible that the mild common cold may have played a significant role in the asystolic episode, for the circulation is known to be less stable during infections. Since fatality did not occur, this case cannot be regarded as indicating the mechanism of sudden death after exertion. For the same reason it cannot substantiate the hypothesis of fatal vasovagal syncope. It does, however, make this concept seem attractive.

SUMMARY

1. While standing erect following an episode of hard physical work, a normal young soldier suffered a syncopal attack during which a cardiac arrest for nineteen seconds occurred.

2. Such an asystole raises again the question whether sudden death during and after physical exertion may be the result of a fatal vasovagal syncope.

It is a pleasure to acknowledge the assistance of Major Edgar A. Blair, Infantry, Army of the United States, in this study, and the technical participation of Tec. 3 Howard Golden and Tec. 4 Wayland James.

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Abstracts and Reviews

Selected Abstracts

Herrmann, G. R.: Cholesterol Levels in Various Diseases and the Effects of Decholesterizing Agents. Texas State J. Med. 42:260 (August), 1946.

Atherosclerosis, once established, has always been considered irreversible. The treatment usually recommended has been indirect or palliative. A definite relationship appears to exist between atheromatous vascular disease and cholesterol metabolism. It is suggested that in the presence of hypercholesterolemia and a permeable intima, small plaques may increase in size by a process of imbibition with the ultimate development of occluding atheromata or rupture with local thrombosis.

A study was made of 120 patients who had coronary thrombosis. This group exhibited high serum cholesterol which was 33 per cent above normal for total cholesterol and 26 per cent above normal for cholesterol esters. There was evidence to indicate that the lowering of the level of cholesterol in the plasma may facilitate the removal of this substance from plaques and reduce the abnormal cholesterol deposits in the vascular system. The possibility of accomplishing decholesterization of tissue deposits has been suggested by many authors. Lipotropic factors, such as pancreatic extracts, lipolysin, lipocaic, choline, and methionine, have been found to be effective in the treatment of fatty cirrhosis that results from a nutritional defect incident to alcoholism.

The authors studied the following regimes: (1) a low-fat diet with potassium iodide (in 13 patients); (2) thyroid extract in daily doses not exceeding 100 mg. (in 18 patients); (3) choline, 1.0 Gm. given three times daily (in 35 patients); (4) methionine, 0.5 Gm. given three times daily (in 4 patients); (5) Inositol, 0.5 Gm. given four times daily (in 9 patients); (6) Berenjena, a powder of *Solanum Melongena* L., 1 Gm. daily (in 4 patients); (7) Alcaucil, a powder of *Cynara Scolymus*, 1 Gm. given three times daily (in 10 patients).

The application of these measures resulted in varying degrees of reduction in the blood level of cholesterol and cholesterol esters. The lipotropic agents produced no disagreeable secondary effects. The patients, with few exceptions, reported that they felt better and that the frequency and severity of their precordial discomfort was reduced.

BELLET.

Melville, K. I.: The Protective Action of Atabrine Against Chloroform-Adrenaline Ventricular Fibrillation. J. Pharmacol. & Exper. Therap. 87:350 (August), 1946.

The author had previously demonstrated the efficacy of coronary vasodilators in preventing the occurrence of ventricular fibrillation following injection of large doses of posterior pituitary extract in dogs under phenobarbital narcosis. In a previous communication he had also shown that atabrine was a powerful coronary vasodilator in the isolated perfused rabbit's heart. He therefore tested the effect of atabrine in preventing the development of ventricular fibrillation as a result of different procedures. The intravenous injection of atabrine was found to be capable of protecting dogs from ventricular fibrillation which follows the administration of chloroform

and adrenaline. This protective action also occurred after double vagotomy or atropinization. The effect of atabrine was found to be exceedingly transitory, even when quantities of the drug are injected slowly into the circulating blood. The data did not permit any definite conclusions concerning the mechanism of the phenomenon. The author suggests that it may depend upon the coronary-vasodilator action of atabrine. This action of atabrine might offset either an initial reduction in coronary flow or some impairment in myocardial nutrition induced by adrenaline under the conditions described.

BELLET.

Farah, A.: Lethal Dose and Average Rate of Uptake of G-Strophanthin in the Heart-Lung Preparation of the Dog Under Varying Conditions. J. Pharmacol. & Exper. Therap. 87:364 (August), 1946.

The author had previously shown that 1 gram of heart in the heart-lung preparation of the dog binds only one minimum lethal dose of g-Strophanthin, regardless of the rate of administration of the drug. In these earlier studies, certain experimental conditions, such as work of the heart, blood temperature, blood volume, and heart rate were kept constant.

The object of the present study was to see whether quantitative and qualitative changes in the work of the heart or changes of blood volume, temperature, or heart rate have any influence on the lethal dose, the minimal lethal dose, or average rate of uptake of g-strophanthin in the heart-lung preparation of the dog.

Reduction in the work of the left heart did not significantly influence either the lethal dose or minimal lethal dose of g-strophanthin. The average rate of uptake was also unchanged, irrespective of whether the work of the heart was high or low. A reduction in the blood volume led to a decrease of the lethal dose of g-strophanthin when high rates of administration were used. As the rate of administration was diminished, the lethal dose approached that determined with the higher blood volume. The reduction in the blood volume does not affect the minimum lethal dose of g-strophanthin although it changes the lethal dose. Reduction of the blood temperature increased the lethal dose and decreased the average rate of uptake and optimal rate of administration. The minimal lethal dose of g-strophanthin was not influenced by changes in the blood temperature from 35 to 39° C.

Sublethal doses of barium chloride and epinephrine did not change the lethal dose, the minimal lethal dose, or average rate of uptake of g-strophanthin in the heart-lung preparation of the dog. Caffein sodium benzoate increased the average rate of uptake but did not increase the minimal lethal dose of g-strophanthin. No differences in sensitivity to digitoxin could be detected between intact anesthetized pups and adult dogs.

BELLET.

Dripps, R. D., and Deming, M. V. N.: An Evaluation of Certain Drugs Used to Maintain Blood Pressure During Spinal Anesthesia. Surg., Gynec. & Obst. 83:312 (Sept.), 1946.

The vascular response of twenty-five hundred patients who received spinal anesthesia was studied. Five hundred patients received no pressor drug prior to anesthesia. In this group the average fall in systolic blood pressure was 36 per cent from the pre-operative level. Five hundred patients received paredrine for the purpose of maintaining blood pressure level. The average fall in this group was 18.6 per cent. Five hundred patients who were given ephedrine showed an average decrease in blood pressure of 14.5 per cent. Five hundred patients who received pitressin-ephedrine showed an average decrease of 5.3 per cent. Five hundred patients who were given methedrine showed a 3.0 per cent decrease in systolic blood pressure. Methedrine and pitressin-ephedrine were therefore the most effective of the drugs used. Methedrine is preferred to pitressin-ephedrine for a number of reasons. The former drug is administered intramuscularly in doses of 20 mg. at the time of lumbar puncture. The onset of action is prompt and the duration is prolonged.

The incidence and degree of the decrease in blood pressure which follows spinal anesthesia is greater with higher levels of anesthesia, in older individuals, and in patients whose initial blood pressures are above normal. There is no difference in vascular response when procaine and pontocaine are used as spinal anesthetic agents.

NAIDE.

Warren, R.: War Wounds of Arteries. Arch. Surg. 53:86 (July), 1946.

Experience with 115 patients with arterial wounds resulted in the following impressions. The critical arteries are the popliteal, the internal carotid, and the common femoral. Others become critical if the collateral circulation has been involved by the wound. Early ligation or ligation for secondary hemorrhage is dangerous. Late or elective ligation is much less so. The chief time for sympathectomy is before operative interruption of a critical artery. Its use as a prophylactic against spasm of collateral arterial supply is its most important function. If there is not time to do a sympathectomy before and this operation can be performed within six hours after such interruption, it is still indicated, but much less benefit can be expected. If sympathectomy is impossible, sympathetic block, repeated as often as practicable, should be used for forty-eight hours. The release from closed spaces, such as the popliteal space, of blood clots or edema through large incisions which are left open is of extreme importance in affording free flow through collateral vessels. In early cases of wounds of critical arteries, the use of venous grafts or prostheses is indicated. In the decision as to whether a graft or prosthesis should be used in a patient having a late or elective ligation, the one most important indication for their use is lack of good arterial back bleeding from the distal stump. A circular bandage should not be used on any limb that has a doubtful circulation.

NAIDE.

Colby, F. H.: Venous Thrombosis and Pulmonary Emboli in Urology. J. Urol. 56:124 (July), 1946.

The incidence of pulmonary embolism on the urologic service at the Massachusetts General Hospital is reported. A comparison is made of the incidence of pulmonary embolism in the years 1939 and 1940 with the incidence in 1943 and 1944. The purpose of the study was to determine whether early ambulation and femoral vein interruption had lessened the incidence of venous thrombosis, pulmonary infarction, and fatal pulmonary emboli. There were approximately one-third as many venous thromboses and pulmonary infarcts in 1943 and 1944, when early ambulation after operation was the rule and femoral vein interruption was practised, as there were in 1939 and 1940, when these measures were not applied. These measures reduced the incidence of fatal pulmonary emboli by two-thirds in the group of patients operated upon for prostatic obstruction. They failed, however, to eliminate these serious complications entirely or even to reduce them to such a degree as to allow the feeling that the patient was free of danger. Despite early ambulation, careful examination of the legs, and detection of small infarcts in the lungs by x-ray study, a mortality from pulmonary emboli of 0.93 per cent occurred in 1943 and 1944. In 1943 and 1944 there were nine bilateral vein interruptions performed on patients with prostatic obstruction. Six were for postoperative thromboses and infarcts and three were performed before prostatic surgery as a prophylactic measure. None of these three patients had fatal emboli. Femoral vein interruption as a prophylactic procedure is now being performed more frequently on selected patients.

NAIDE.

Goodman, E. N., Messinger, W. J., and White, J. C.: Indications and Results of Surgery of the Autonomic Nervous System in Naval Personnel. Ann. Surg. 124:204 (Aug.), 1946.

Raynaud's syndrome, hyperhydrosis, and hypertension are often encountered in unstable emotional individuals or in those having high vasomotor tone. The psychologic experiences of military life accentuate these phenomena and the transition from military to civilian life in turn may evoke similar responses.

Fifty-three patients are reported in whom preganglionic sympathectomy was performed for various peripheral vascular conditions and a more extensive sympathectomy for hypertension. The results obtained in Raynaud's syndrome, as well as in thromboangiitis obliterans, arteriosclerosis, and vasospasm, following wounds of major arteries, were uniformly good. Good results were also obtained in hyperhidrosis, in thrombophlebitic complications with vasospasm, and in painful states such as causalgia, certain amputation stump neuralgias, and angina pectoris. Conclusions concerning the effects of surgical intervention in hypertension are limited by the lack of long follow-up studies, but the immediate results on patients observed over a period of two years are significant lowering of blood pressure, relief of distressing headaches, nervousness, and irritability, and rehabilitation to useful occupations. No fatalities or serious complications have resulted from the operative procedures. NAIDE.

Hines, E. A., Jr., and Farber, E. M.: Ulcer of the Leg Due to Arteriosclerosis and Ischemia, Occurring in the Presence of Hypertensive Disease (Hypertensive-Ischemia Ulcers): A Preliminary Report. Proc. Staff Meet., Mayo Clin. 21:337 (Sept. 4), 1946.

A series of eleven cases is reported in which leg ulcers were associated with hypertensive disease of long duration and considerable sclerosis of the retinal arterioles of the chronic hypertensive type. The authors postulate that changes similar to those in the retinal arterioles may also occur in the small arteries of the skin and subcutaneous tissues and give rise to small areas of infarction of the skin. As a result of trauma or for some unknown reason, the skin may break down with consequent formation of an ischemic ulcer. In only two of the eleven cases was there any evidence of occlusive disease in the larger arteries of the extremities. In these two cases the arterial pulsations were diminished but not absent, and no evidence of gross arterial insufficiency was found.

The ulcers were located on the lateral surface of the ankle or lower part of the leg and ranged in size from about 1 to 7 cm. in diameter. The ulcer usually had a purpuric base and in five cases was surrounded by a purpuric circle. The ulcers were usually superficial and had a rather punched-out appearance. The base appeared to be ischemic and granulation was not extensive. The ulcer was usually painful when fully developed. When healing finally began, it progressed slowly and from one to six months passed before the lesion healed entirely.

Histopathologic study of the ulcers and adjacent skin in five cases revealed organic changes in the arterioles. The most common changes were an increase in the thickness of the arteriolar wall and a decrease in the diameter of the lumen.

In none of the cases was there a history of thrombophlebitis. Furthermore, the lesions in this group were located in regions not commonly involved in chronic venous insufficiency; that is, on the lateral surface of the leg, in contrast to the usual location of stasis ulcers which is low on the medial surface of the leg.

In addition to chronic venous insufficiency, the following conditions should also be ruled out by pathologic study before the diagnosis of hypertensive ischemic ulcer is made: occlusive arterial disease, syphilis, blood dyscrasia, cutaneous sensitivity to drugs, frostbite, seasonal variations affecting the occurrence of the lesions, and serious local injury or other disease. NAIDE.

DeTakats, G., Graupner, G. W., Fowler, E. F., and Jensik, R. J.: Surgical Approach to Hypertension. Arch. Surg. 53:111 (Aug.), 1946.

The results of the surgical treatment of hypertension, based on the pre-operative and post-operative study of fifty-two patients, are discussed in detail. For an improvement in the results of surgical treatment, a rigid selection of cases is advocated. The patients fall into three groups.

Group 1 includes patients who present a clear-cut indication for surgical treatment. There should be a persistent casual hypertension of over 140 systolic and 90 diastolic in persons between 18 and 25 years of age before operation is considered. Patients in Group 1 are predominantly asymptomatic and the hypertension is recognized at pre-employment, pre-induction, or insurance examinations. A distinction should be made between the hypertension of patients in Group 1 and the hypertension of adolescents who may come from hypertensive families and who, during

their period of growth when increased pluri-glandular function is increased, show an elevated pressure which may become normal in early adult life. For patients in Group 1, frequent re-examinations are advised at three-month intervals. No type of medical treatment seems effective in preventing the occurrence of typical juvenile hypertension. It is in this group, the members of which have minimal or no organic changes, that the best results were obtained by extensive sympathectomy. Of the seventeen patients in Group 1 who were operated upon, only two had recurrent hypertension which was corrected after completion of a technically incomplete operation.

Group 2 is one in which the indication for surgery is relative and debatable. This group consists of the middle-aged hypertensive patients who are beginning to show symptoms and evidence of organic damage. Twenty-four patients in this group were treated surgically. Of these, six showed recurrence of hypertension. These six were analyzed and found to have either striking enlargement and rigidity of the aorta or the continuous vasospasm of severe benign nephrosclerosis or pyelonephritis which must be regarded as the pre-malignant phase.

Group 3 consisted of ten patients with pre-malignant and malignant hypertension. These patients are not suitable for operation, despite the occasional spectacular results reported in the literature. The argument, frequently brought forward, that all other types of treatment have failed, and that the patient has nothing to lose since his prognosis is so poor, is not a valid one; operation in this series has been found to be useless in this type of patient.

This study also does not bear out the observation of other investigators that a marked drop in blood pressure with high spinal anesthesia denotes that a good result can be expected from extensive sympathectomy. In operating on a large number of older arteriosclerotic patients with hypertension under spinal anesthesia, severe fall in blood pressure has been repeatedly observed. Such patients, however, could hardly be regarded as suitable for sympathectomy.

Patients with pyelonephritis, post-toxemic hypertension, streptococcic nephritis, and rheumatic reno-vascular damage are favorable candidates for surgery, provided the vascular damage is not too far advanced. On the other hand, the "neurogenic" group has not done well. The fluctuations of their pressures have not been abolished and their emotional hypothalamic "outbursts" are not eliminated and continue to operate upon the vascular system.

The value of renal biopsies is discussed and also the help afforded by special post-operative studies including roentgenograms of the chest, electrocardiograms, tests of epinephrine sensitivity, and estimates of circulation time. The redistribution of circulation due to the effect of splanchnic nerve section on blood depots is stressed. So far, no single or combined method of treatment can be recognized which gives rigidly selected patients with hypertension as much benefit as the transdiaphragmatic splanchnic nerve section combined with dorsolumbar sympathetic ganglionectomy.

NAIDE.

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THE American Heart Association was founded in 1924 "for the study of and the dissemination and application of knowledge concerning the causes, treatment and prevention of heart disease; the gathering of information on heart disease; the development and application of measures that would prevent heart disease; seeking and provision of occupations suitable for heart disease patients; the promotion of the establishment of special dispensary classes for heart disease patients; the extension of opportunities for adequate care of cardiac convalescents; the promotion of permanent institutional care for such cardiac patients as are hopelessly incapacitated from self-support; and the encouragement and establishment of local associations with similar objects throughout the United States."

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The American Council on Rheumatic Fever, organized in 1944, consists of a group of representatives of all national medical organizations concerned with rheumatic fever. It operates administratively through the American Heart Association and carries out the program of the American Heart Association insofar as that relates to rheumatic fever.

Annual membership in the American Heart Association is \$2.50 and includes twelve issues of *Modern Concepts of Cardiovascular Disease*; Journal membership is \$10.00 and includes a year's subscription to the AMERICAN HEART JOURNAL (January-December), twelve issues of *Modern Concepts of Cardiovascular Disease*, and annual membership in the Association. Contributing membership starts at \$25.00 per year; patron membership is \$50.00 and over per year. Membership blanks will be sent upon request.

The Association earnestly solicits your support and suggestions for its work. Donations will be gratefully received and promptly acknowledged.

ANNUAL MEETING

The Annual Meeting and Twentieth Scientific Sessions of the American Heart Association will be held in Atlantic City, N. J., June 6 and 7, 1947. The Hotel President will be the headquarters for all meetings. On June 6, a meeting will be held with representatives of local Heart Associations to discuss the administrative structure of the American Heart Association with particular reference to program. The annual meeting of members will also be held on that day. The scientific sessions will take place on June 6 and 7. The annual dinner is scheduled for Saturday evening, June 7, at the Hotel President. Meetings begin at 9:00 A.M. each day, and members should plan to arrive on June 5. Hotel rooms will be in great demand and every member who wishes to attend is urged to make reservations immediately.

The chairman of the Program Committee for the Annual Scientific Sessions of the American Heart Association is Dr. Edgar V. Allen, Mayo Clinic, Rochester, Minn. All who desire to present papers at the meetings of June 6 and 7 in Atlantic City should forward to him an abstract of the proposed presentation of not more than 300 words. The deadline for the receipt of abstracts is March 30, 1947.

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Original Communications

PULMONARY (VENOUS) AIR EMBOLISM

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ALTHOUGH pulmonary air embolism is relatively infrequent in medical practice, it is so catastrophic when it does occur that further investigation into its etiology, pathologic physiology, prophylaxis, and treatment is fully warranted. Moreover, as recently emphasized by Martland,¹ its importance, from the standpoint of frequency, may be much greater than has been recognized, since very few of these accidents are likely to be reported, and, in other instances in which an autopsy is not done, death may be attributed erroneously to heart disease or some other condition.

DIFFERENTIATION OF PULMONARY AND ARTERIAL AIR EMBOLISM

Basic to an understanding of pulmonary (venous) air embolism is a clear conception of its differentiation from the arterial form of air embolism. Although both depend for their effects on the presence of air in the circulation, the site of entrance of the air determines its distribution within the vascular system and is therefore extremely important. In the pulmonary form, air enters one of the systemic veins and is carried to the right heart and pulmonary circulation and depends for its effects upon mechanical obstruction of the outflow tract of the right ventricle as will be explained subsequently. Fairly large amounts of air are needed to produce this effect. In arterial embolism, on the other hand, the air gains entrance to the pulmonary venous channels and is propelled from the left ventricle to those systemic arteries which supply the superiorly located

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portions of the body. Since a small amount of air can effectively block a medium-sized artery, serious consequences may result when a few cubic centimeters of air enter the pulmonary vein and are carried into either the coronary, or cerebral circulation, or both. Our studies² have shown that as little as 0.025 c.c. of air injected directly into the anterior descending branch of the left coronary artery of a dog can produce an ischemic disturbance in the myocardium supplied by that artery, and an increase of the amount injected to as much only as 0.05 c.c. may cause death of the animal.

• As would be expected from what has already been said, the clinical picture in the two forms of embolism is totally different. In the pulmonary, or venous form, the presence of air in the right ventricle produces a loud, churning sound, often readily heard without stethoscopic aid, which is known as the "millwheel" murmur. This murmur appears almost immediately after air has entered the venous circulation. As a result of the obstruction of the right ventricular out-flow tract from the air trap which forms within it, the venous pressure rises to a marked degree, and cyanosis becomes readily apparent. Associated with these retrograde circulatory effects, there also appear the manifestations of forward circulatory failure, namely, a falling blood pressure, a rapid thready pulse, and syncope due to cerebral ischemia. As will be explained later, we have discovered in our experiments that all of these manifestations are profoundly influenced by position of the body.

In the arterial form, the clinical picture is dependent upon ischemia in vital organs, especially the heart and brain. If the head is higher than the level of the arch of the aorta, air will enter the cerebral circulation and cause various neurological manifestations, such as aphasia, blindness, hemiplegia, or monoplegia. Examination of the fundus oculi may be of great diagnostic value in such cases since air bubbles may be observed in the retinal vessels.³ Of further diagnostic value is the observation of a marbled appearance of the skin indicating involvement of the superficial vessels. The demonstration of "air bleeding" which can be accomplished by making a small incision in the skin over the most superior portion of the body is conclusive evidence of this form of air embolism.⁴ Involvement of the coronary arteries is probably an important factor in causing death in these cases. Myocardial infarction has been demonstrated by electrocardiography,⁵ and post-mortem and experimental evidence have also shown the importance of involvement of these vital arteries.⁶⁻⁹

The position of the body is much less important therapeutically in arterial air embolism than in the pulmonary form. The head down position does *prevent* cerebral involvement if the patient is in that position when the embolism occurs, but it does not cause a clearing of the cerebral manifestations if the position is assumed only *after* the accident has taken place. Furthermore, it does not prevent coronary artery involvement.

A summary of these differences between pulmonary and arterial air embolism is presented in Table I. Subsequent discussion in this paper will deal entirely with *pulmonary* air embolism.

TABLE I. DIFFERENTIATION OF PULMONARY (VENOUS) AND ARTERIAL AIR EMBOLISM

	PULMONARY	ARTERIAL
Site of entrance of air	Peripheral veins	Pulmonary veins
Procedures responsible	Surgical Obstetrical Diagnostic or therapeutic air insufflation	Thoracentesis Pneumothorax Thoracic surgery
Fatal dose of air	Large	Small
Cause of death	Air trap— Pulmonary conus	Cerebral embolism Coronary embolism
Favorable position	Left lateral	Head down
Signs	Mill wheel murmur Increased venous pressure	Air bleeding Fundus examination Marbled skin
Blood pressure	Lowered	Elevated (initially)

ETIOLOGY OF PULMONARY AIR EMBOLISM

Air may enter the systemic veins in sufficient quantity to produce serious embolic manifestations under a number of different circumstances.¹⁰ These may be summarized as follows:

A. Surgical

1. Operations involving veins of neck
2. Operations involving dural sinuses
3. Uterine curettage

B. Diagnostic air injections

1. Into the perirenal area
2. Into the peritoneal cavity
 - a. Direct
 - b. Transuterine (Rubin test)
3. Into the urinary bladder
4. Into the joints

C. Therapeutic air injections

1. Maxillary antrum lavage
2. Pneumoperitoneum
3. Vaginal insufflation by powder blowers

D. Obstetrical

1. During delivery of patients with placenta previa

E. Accidental entrance of air into intravenous apparatus
(This accident is rare)

A detailed analysis of each of these circumstances is unnecessary, but several of them deserve additional emphasis. It is of especial interest to note that the injection of air into the perirenal area, a procedure which is admittedly of great value in the diagnosis of adrenal tumors, has been abandoned in many clinics because of the frequency with which air embolism occurs during this procedure despite careful technique. Another fact worth noting is that, of all the veins of the body, the uterine sinuses are probably the most vulnerable to the entrance of air, a circumstance which makes obstetrics and gynecology the specialties in which this complication is most to be feared. A particularly impressive demonstration of this vulnerability is provided by the recently reported deaths from air embolism which have resulted from the simple procedure of vaginal insufflation for trichomonas infestation.¹¹⁻¹⁴ This has occurred especially when the treatment has been used during pregnancy, but it has also been observed in nonpregnant individuals near the time of menstruation.

EXPERIMENTAL STUDIES

The studies to be reported in this communication were carried out in order to obtain more complete information than has heretofore been available concerning the mechanism of death in pulmonary air embolism and to attempt to discover means of preventing this occurrence. Not only have the studies fulfilled this purpose, but they have also provided information of great interest concerning electrocardiographic changes associated with acute right ventricular dilatation and with ischemia involving the right ventricular musculature.

Experimental Procedure.—The dog was used as the experimental animal. Sodium pentothal, 20 mg. per kilogram of body weight, and sodium barbital, 150 mg. per kilogram of body weight, were administered intravenously for anesthesia. Ten animals received air injections into the femoral vein with the thorax intact, standard electrocardiograms being taken before and at intervals after the injection. In ten other animals, which were given artificial respiration, the thorax was opened by a sternum-splitting incision and direct observation of cardiac changes was made following the injections of air into the femoral vein. In seven of these, electrocardiograms were taken by means of a direct lead from the right ventricular muscle adjacent to the anterior descending branch of the left coronary artery. This electrode was paired with one attached to the left hind leg. In three animals leads from the right ventricular cavity were obtained. The use of a cardioscope permitted constant observation of the electrocardiographic changes, and film recordings were taken as indicated.

Following the completion of the experiment, careful autopsy study was made to determine the distribution of the air in those animals in which the thorax was intact.

OBSERVATIONS

Experiments With Intact Thorax.—Following the injection of from 25 to 150 c.c. of air into the femoral vein, a gallop rhythm and a loud millwheel murmur which was audible without a stethoscope were heard over the precordium. Tachy-

cardia, marked tachypnea, cyanosis, and elevation of the venous pressure were then noted. Whether or not fatality occurred depended on factors to be discussed later. Several animals tolerated repeated injections of as much as 100 c.c. of air at intervals of five to ten minutes.

Experiments With Open Thorax.—Observation of the heart through a sternum-splitting incision in ten experiments showed an extremely interesting succession of events following the femoral air injection. The same millwheel murmur was heard as in the experiments in which the thoraces were intact. Tachypnea was, of course, not observed, since the animals were receiving artificial respiration. Almost immediately following the injection of air, there was noted a sudden marked dilatation of the right auricle and ventricle associated with the rise in venous pressure which had been observed in the intact thorax experiments. With the marked dilatation of the right ventricle, which was especially profound in the outflow tract region, there developed an area of readily observed ischemia just to the right of the lower reaches of the anterior descending branch of the left coronary artery. This ischemic region is shown as a shaded area in the drawing (Fig. 1) made from a photograph of one of the animal hearts. The most ventral

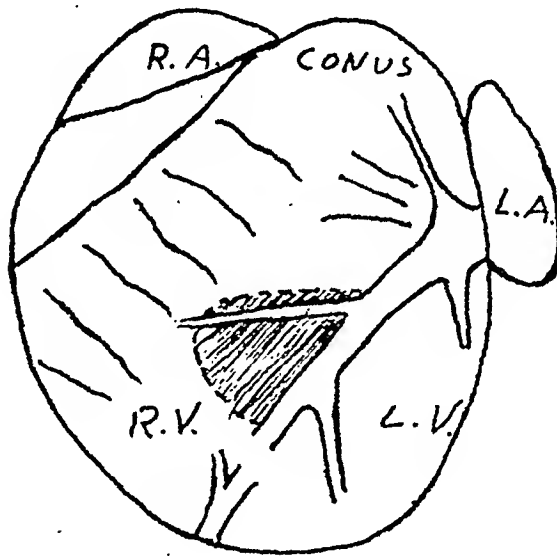


Fig. 1.—Drawing made from photograph of dog's heart showing area of ischemia (shaded area) located to the right of the anterior descending branch of the left coronary artery.

portion of the right ventricular outflow tract was found by transillumination to contain a large air bubble. In these open chest experiments, survival was much less likely; and, even with relatively small amounts of air (25 to 50 c.c.), the right ventricular dilatation continued and the contractions became more and more feeble until death supervened. If, however, the animal was turned onto his left side before the dilatation had become extreme, the contractions of the right ventricle again became strong and the animal recovered. This remarkable recovery from seemingly irreversible right ventricular failure was associated with disappearance of the large air bubble previously present in the region of the pulmonary conus and artery, these regions no longer being superiorly located with respect to the other portions of the right ventricle.

FACTORS INVOLVED IN FATALITY IN EXPERIMENTAL PULMONARY
AIR EMBOLISM

No attempt was made in these experiments to determine the fatal dosage of air in relationship to body weight, as has been done by others.¹⁵ Our experience has been that the dosage which will produce fatality is extremely unpredictable, and, while there is undoubtedly some relationship to the size of the animal, many other factors are involved which greatly complicate any attempt at calculation. It is our belief that the cross-sectional area of the right ventricular outflow tract at its most superior point, (this point will depend upon the position of the animal) is probably much more closely related to the fatal dosage than is the weight of the animal.

The factors which we have found to be most closely related to mortality can be summarized as follows:

1. *The amount of air injected.* As already stated, this is undoubtedly a very important factor, but it is so modified by others as to make the calculations of a dosage/weight relationship for all circumstances an impossibility.

2. *The speed of the injection.* We have found that tremendous quantities of air can be injected without fatality if sufficient time is taken for the injection. Thus, one animal survived a total of 1,000 c.c. of air which was injected in amounts of 100 c.c. at intervals of five to ten minutes. Not all animals, however, will tolerate such a procedure.

3. *The position of the animal.* This is a tremendously important factor, we believe, and one which has not been mentioned in any of the previous studies of this subject. We have found that an animal can tolerate more air when lying on his left side than can be tolerated in any other position. Furthermore, if an animal is allowed to develop evidence of marked right ventricular failure while lying on his back, and is then turned onto the left side, recovery frequently follows immediately. As we have already pointed out, the return of forceful right ventricular contractions under these circumstances is dramatic. Conversely, the right lateral position is by far the worst position of all for the animal. It is of interest that tachypnea does not occur when the animal is in this latter position.

An explanation for the recovery of animals when turned into the left lateral position is to be found in the observations made in the open chest experiments. These have shown that the right ventricle labors against the obstruction of an air trap in its outflow tract when the position of the animal is such as to make this the most superior portion of the right heart. Such would be the case with the animal on his back or on his right side. When turned onto the left side, however, the outflow tract assumes a position inferior to the body of the right ventricle. The air trap then disappears from this, now inferior, position and is presumably churned into a froth which is mixed with the blood in the right ventricular cavity. The obstruction to the circulation is thus relieved and blood can be propelled into the pulmonary vessels by the now unimpeded right ventricular contractions. The froth gradually disappears from the cavity of the right ventricle, and it must be assumed that it has been transported into the lungs with the blood where excretion can take place.

4. *The effectiveness of the pulmonary excretory mechanism.* As previously explained, tachypnea failed to occur under two circumstances in our experiments. It was absent in the intact thorax experiments when the animal was on his right side, and it was absent in the open chest experiments with artificial respiration. It was under these two conditions that the smallest amounts of air were found to be fatal. It would seem, then, that the tachypnea ordinarily present with air embolism acts in some manner as a protective mechanism and tends to prevent death.

Cause of the Myocardial Ischemia.—The ischemia of the right ventricular musculature which was noted in the open chest experiments requires reference to the work of Visscher¹⁶ for its explanation. This investigator has shown that the flow of coronary blood depends on a pressure gradient measured by the differences in pressure between the aorta at one end of the coronary circuit and the coronary sinus and right ventricle at the other end. Furthermore, the *relative* amount of blood flow to the coronary sinus and to the right ventricle (thru the thebesian channels) is determined by the aorta-pulmonary artery pressure difference. The greater this pressure difference, the greater the thebesian flow and the less the coronary sinus flow. With a low aorta-pulmonary artery pressure difference there will be a great falling off of the thebesian flow. Since the right ventricular muscle is particularly dependent upon the blood which traverses the coronary-thebesian circuit for its nourishment, it is the right ventricle which is especially vulnerable to increased pressure in its outflow tract, in contrast to the left ventricle which can tolerate increased loads for long periods of time. When the pressure within the right ventricular cavity is markedly increased, as in our air embolism experiments, the thebesian flow is greatly restricted. At the same time, there is a reduction in the aortic pressure, and these two factors combine to reduce markedly the aortic-right ventricular pressure gradient so that blood flow to the muscle of the right ventricle is impaired and gives rise to ischemia. Why this ischemia is grossly evident in only one part of the right ventricular muscle we are unable to determine at the present time.

ELECTROCARDIOGRAPHIC CHANGES

The standard electrocardiogram in the ten closed thorax experiments demonstrated striking alterations at the time when the circulatory disturbances were at their height. These consisted in marked depressions of the S-T segments in Leads II and III without complete obliteration of the upright T waves (Fig. 2). No change in the S-T segment in Lead I was noted. Disturbances in rhythm, consisting in varying degrees of A-V block or the development of nodal rhythm, were not infrequent. The deviation of the S-T segments disappeared rapidly when recovery from the embolic disturbance occurred.

In the ten open chest experiments, the opportunity was afforded to lead directly from the area of ischemia previously described and outlined in Fig. 1. This was done in seven experiments and an invariable sequence of marked changes occurred. These changes are shown in tracings from a representative experiment (Fig. 3). It will be seen that, almost immediately following the

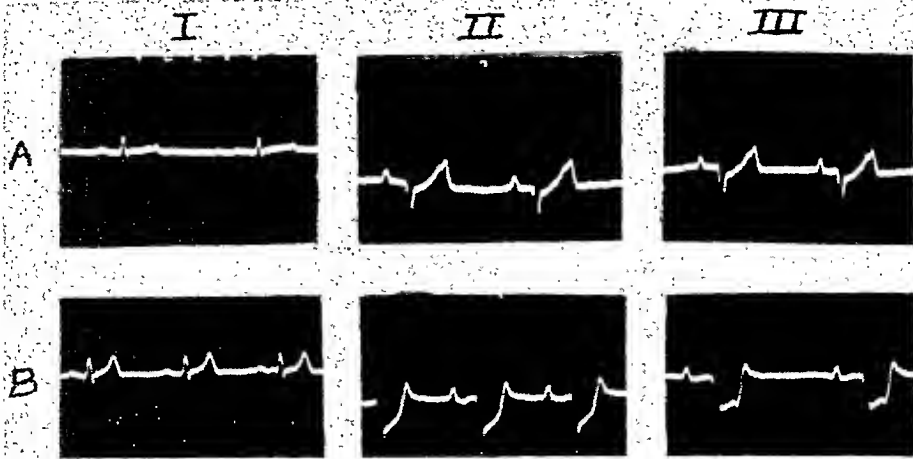


Fig. 2.—Standard electrocardiograms in closed thorax experiment before (A) and after (B) the injection of 100 c.c. of air into the femoral vein of a dog. Marked changes in S-T segments in Leads II and III are shown in B.

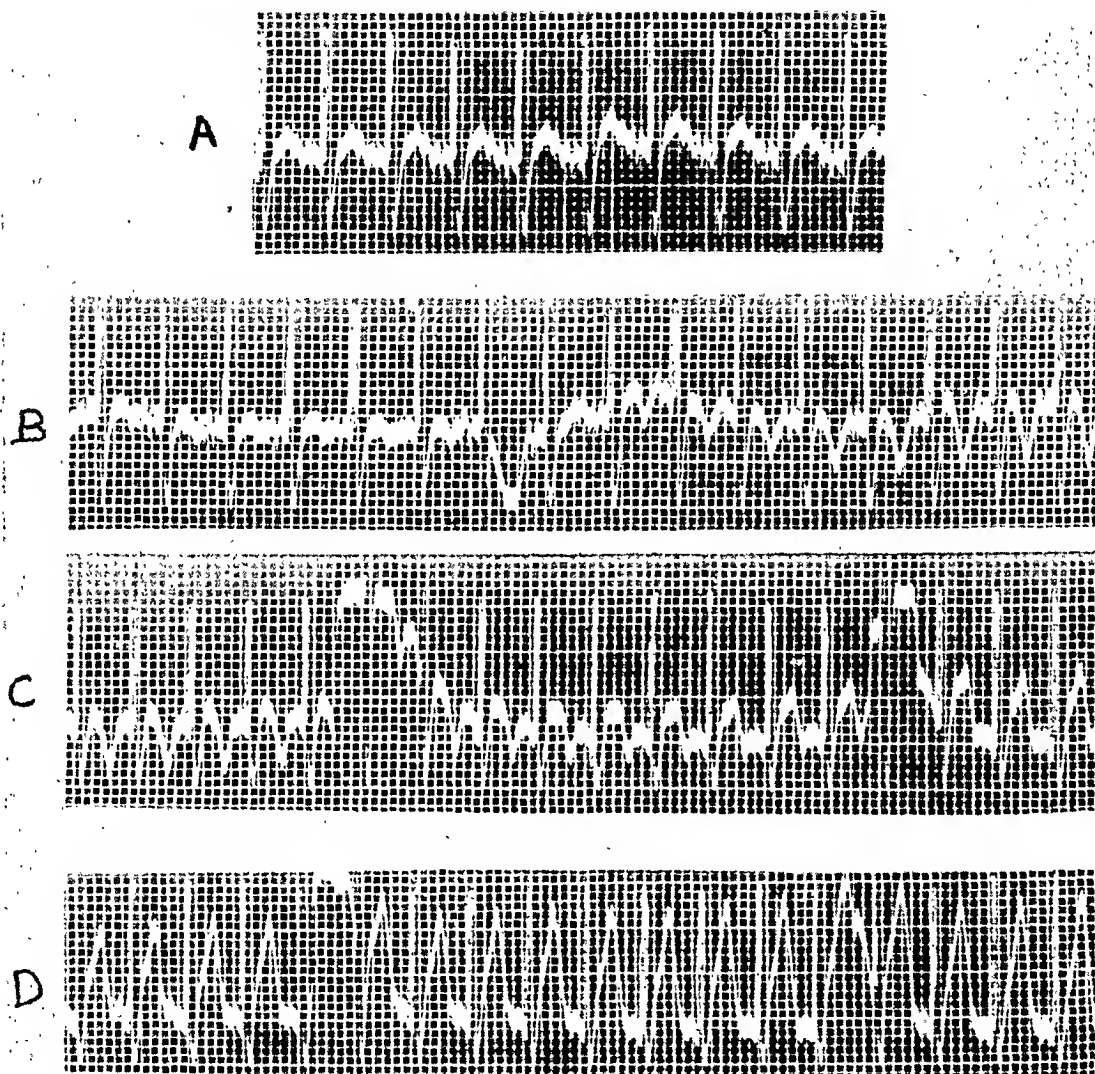


Fig. 3.—Open thorax experiment. Exploring electrode on ischemic area. Indifferent electrode on left hind leg. Positivity of exploring electrode represented by upstroke. Appearance and disappearance of ischemia-injury pattern well shown.

A: Control, thorax open. B: Immediately after the injection of 30 c.c. of air. C: Ten seconds after the end of B. D: Immediately after C. E: Sixteen seconds after D. F: Twenty-one seconds after E. G: Dog turned onto left side. Sixty-six seconds after F. H: Following recovery. T waves subsequently became upright. (The R waves have been retouched in this figure.)

injection of air, sharp inversion of the T wave takes place (Fig. 3, *B*). Ten seconds later (Fig. 3, *C*), an elevation of the S-T segment makes its appearance and, as it gradually becomes more marked, the T-wave inversion disappears. There then develops a more and more extreme S-T segment deviation. When this attains a maximum (Fig. 3, *F*), elevation of the S-T segment considerably

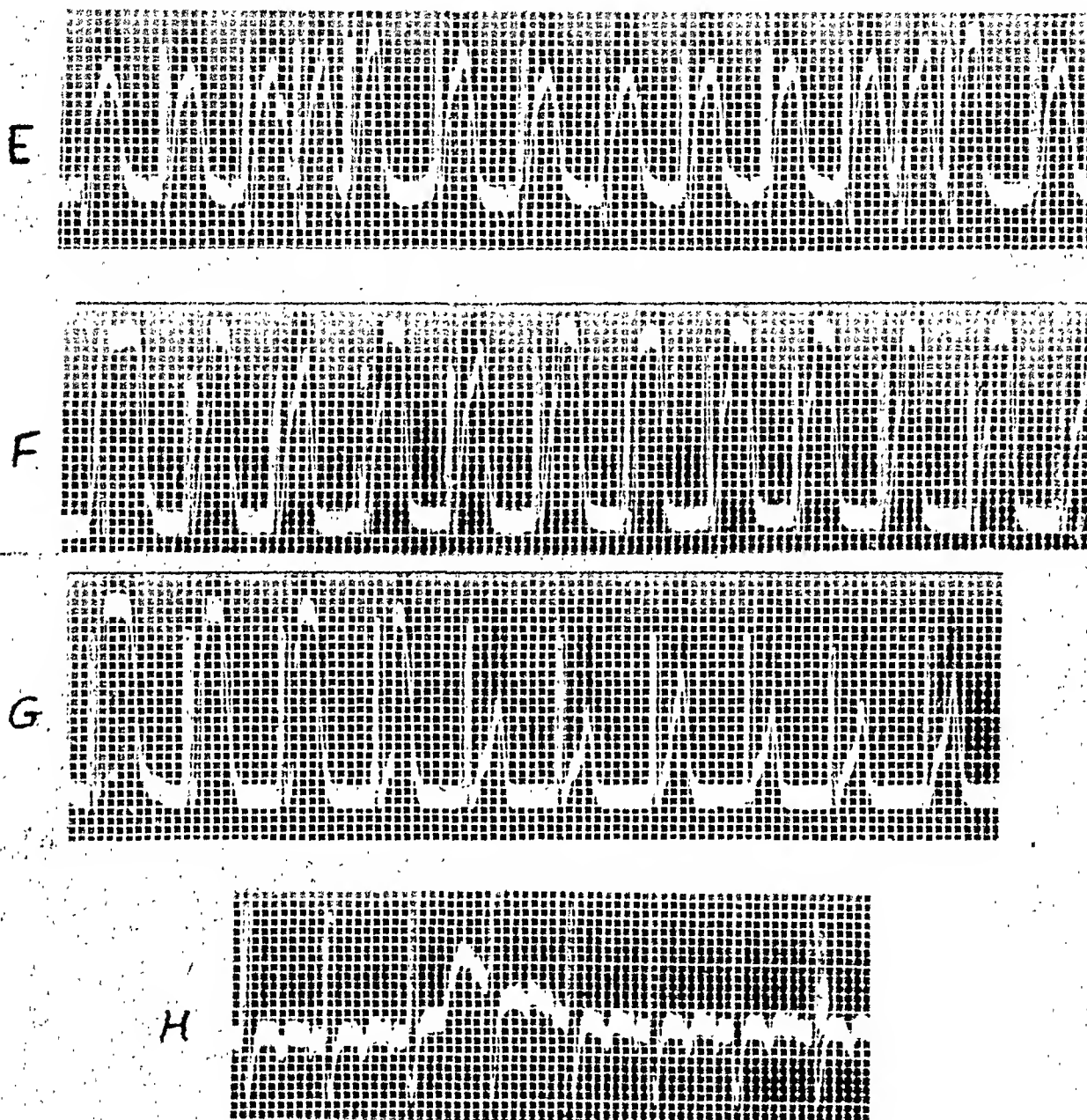


Fig. 3 (Cont'd.).—For complete legend, see opposite page.

surpasses the R wave in height. There is also some change in the QRS complex which consists in the disappearance of the normal S wave. When the animal was turned onto his left side in this experiment, the previously noted changes disappeared rapidly in the reverse order (Fig. 3, *G*). In tracings that followed those shown in Fig. 3, *H*, there was a return of the normal upright T wave.

The sequence of changes described is identical with that observed by Bayley and LaDue¹⁷ in studies of the ischemia-injury pattern induced by subtotal,

temporary occlusion of a coronary artery. In their studies, as in ours, inversion of the T waves (first stage ischemia) preceded the appearance of S-T segment deviation (second stage ischemia-current of injury phase). Bayley and LaDue were not able, however, to obtain as complete a reversal of changes as occurred in these experiments.

In addition to the changes in the final ventricular deflection which have been described, marked alterations in the QRS complex were observed in three experiments. An example of these changes is shown in Fig. 4. The same sequence

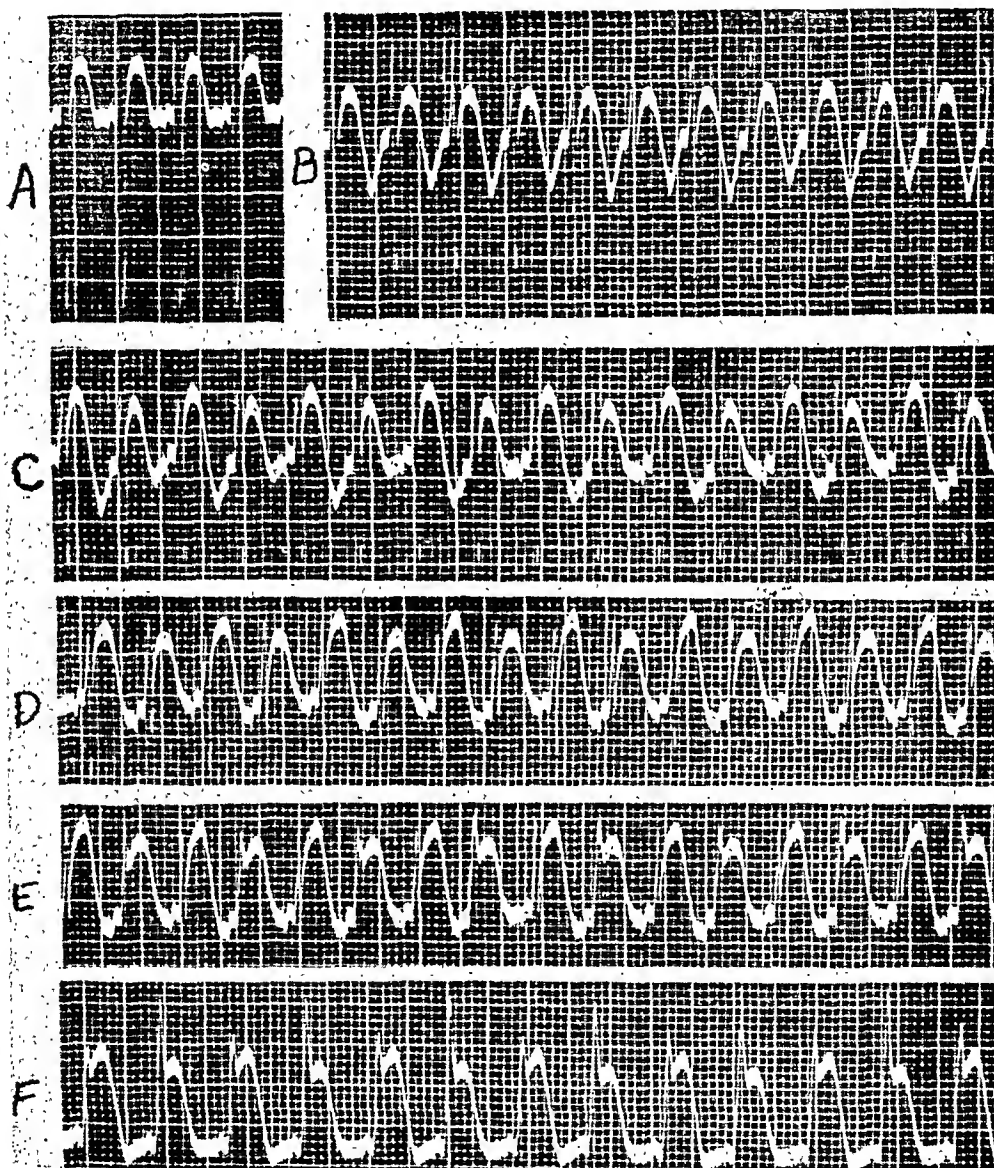


Fig. 4.—Open thorax experiment. Same technique as in Fig. 3. Demonstrates gradual development of right ventricular conduction defect.

A: Control, thorax open. B: Immediately after the injection of 30 c.c. of air. C: Immediately following B. D: Twenty seconds after C. E: Ten seconds after D. F: Forty-five seconds after E. For description of changes see text.

of events involves the S-T segment, the T waves, and the ischemia-injury pattern that are shown in Fig. 3. The animal was not allowed to recover, however, so there is no reversal of these changes. With reference to the QRS complex, the same gradual disappearance of the S wave is observed, and, during the progress of this disappearance, an electrical alternans occurs in which there is a reciprocal relationship between the depth of the S wave and the height of R. When the disappearance of the S wave has become complete (Fig. 4, *E*), there is seen to be a notching of R, or a second positive upstroke in the QRS complex. In the last tracing (Fig. 4, *F*), the height of the R wave has considerably increased, and there is also increased width. Thus, there is observed the development of considerable delay in complete activation of the musculature subjacent to the electrode, since the activating impulse is still travelling toward the electrode at the end of ventricular excitation, whereas in the control tracing (Fig. 4, *A*) the activation of the subjacent musculature was complete at a time when much of the remainder of the myocardium had yet to be activated (as indicated by the large S wave).

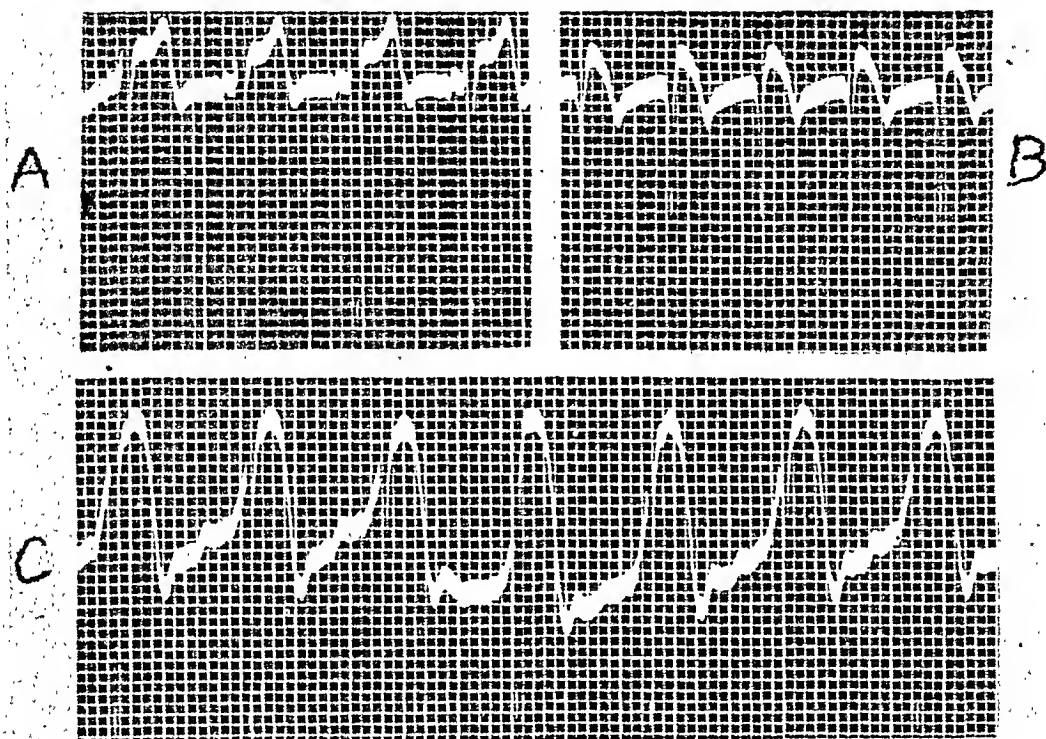


Fig. 5.—Open thorax experiment. Exploring electrode leading from right ventricular cavity. Indifferent electrode on left hind leg.

A: Control. Electrode within right ventricular cavity. B: After injection of 30 c.c. of air. Early ischemia pattern well shown by T-wave inversion. C: Two minutes after B. Large broad initial upstroke now present in QRS complex.

In order to determine whether or not the delay in activation of the right ventricular muscle under the electrode was due to a septal effect, three experiments were performed using an electrode within the cavity of the right ventricle according to the method of Wilson and co-workers.¹⁸ The results of these experiments were similar and are represented by the tracings shown in Fig. 5. The control tracing (Fig. 5, *A*) shows a very small initial upward deflection, as is

often the case normally within the right ventricle, due presumably to a slightly later activation of the right side of the ventricular septum than of the left. Following air embolism (Fig. 5, *B*), T-wave inversion is again noted, followed by S-T segment elevation (Fig. 5, *C*), exactly as in leads from the epicardial surface of the heart. The striking feature of the tracing shown in Fig. 5, *C*, however, is the appearance of a large, broad upstroke at the beginning of the initial ventricular deflection. The possibility that this finding represents the development of right bundle branch block must be seriously considered. This is of especial interest since acute dilatation of the right ventricle in man, due to solid pulmonary emboli (acute cor pulmonale), has been shown to produce temporary right bundle branch block in some instances.¹⁹

SUMMARY

Pulmonary (venous) air embolism is a catastrophe which may occur under a variety of circumstances in medical practice. It must be distinguished from arterial air embolism. Our studies in the experimental animal have shown that important factors in determining whether death or survival will occur are: (1) the amount of air which gains admission to the circulation, (2) the speed with which it enters, (3) the position of the body at the time of the embolic accident, and (4) the efficacy of the respiratory excretory mechanism. Death, when it occurs, is due to circulatory obstruction resulting from an air trap in the right ventricular outflow tract. Displacement of the air trap by turning the body into the left lateral position may be life saving even after the right ventricular contractions have become feeble and death seems imminent.

Pulmonary air embolism provides a valuable means of studying experimentally the effects of acute right ventricular dilatation produced by obstruction. The rapid and profound electrocardiographic changes which occur under these circumstances include an excellent demonstration of the effects of myocardial ischemia, and also, in some instances, the demonstration of right ventricular conduction defects. The observations of Bayley and LaDue concerning the ischemia-injury pattern are confirmed.

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THE HEART IN UREMIA

AN ELECTROCARDIOGRAPHIC AND PATHOLOGIC STUDY

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PATIENTS with uremia tend to show marked changes in the electrocardiogram. The role of the uremic intoxication in the genesis of these alterations is difficult to determine since uremia is usually the terminal phase of a long-lasting and progressive disease which affects the heart muscle and gives rise to various electrocardiographic changes long before the uremic changes set in. During the past decade we have become more familiar with the electrocardiographic patterns resulting from these conditions preceding or concomitant with uremia and thus are able to evaluate the factors that determine the final changes during the uremic stage. We are familiar with (1) the different patterns of chronic left heart strain and its improved and simplified diagnosis by multiple chest leads,¹ (2) the electrocardiographic patterns associated with disease of the coronary arteries, (3) the changes produced by diffuse pericarditis, and (4) the changes seen in acute glomerulonephritis; finally, (5) we have learned to recognize the effect on the electrocardiogram of hypocalcemia and hyperpotassemia. Bearing in mind the complexity of the problem, an attempt was made to study the electrocardiographic changes in a group of uremic patients who came to autopsy and to correlate the electrocardiographic with the pathologic findings. The study of the pathologic changes of the myocardium was considered to be important not only in relation to the electrocardiogram, but also in view of the paucity and discordance of previous reports on the pathologic cardiac changes in uremia.

MATERIAL AND METHOD

With the exception of two cases (Cases 26 and 27), the twenty-seven cases studied (Table I) were consecutive necropsied cases with a clinical diagnosis of uremia and with one or more electrocardiograms taken during the uremic stage. The last electrocardiogram in these patients was taken anywhere from eight weeks to less than twenty-four hours ante mortem. In thirteen, only a single record

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was taken and, in the remaining ones, from two to seventeen records taken over a period of from ten days to fourteen years were available. A complete autopsy was performed in all cases and numerous sections were taken from different parts of the myocardium, fixed in formalin, and stained with hematoxylin and eosin. Sudan III stain for fat was used in about one-half of the cases. In every instance where pericarditis was present, particular attention was paid to the adjacent myocardium.

✓The electrocardiograms were analyzed objectively, without knowledge of the autopsy findings, and the abnormalities listed (Table I); in every case the record was specifically examined for evidence of left heart strain (chronic left ventricular strain), myocardial infarction, pericarditis, hypocalcemia, and hyperpotassemia. Then electrocardiographic interpretation and anatomic findings were compared to determine the extent of agreement. Discrepancies were specifically noted.

CLINICAL FINDINGS

✓The clinical data are summarized in Table I. Twenty of the twenty-seven patients in this series were men and seven were women. Most patients were between 40 and 60 years of age; the average age was 47 years.

The nonprotein nitrogen ranged between 57 and 300 mg. per 100 c.c. of blood (with an average of 135) and was above 90 mg. per 100 c.c. in all but three patients. In the three exceptions it was slightly below that level but was rapidly rising and was associated with other unmistakable signs of uremia. The creatinine level was often determined and was always elevated. The systolic arterial blood pressure ranged between 135 and 260 mm. Hg (with an average of 194 mm.). The diastolic pressure was elevated in all but six instances. Many patients presented a severe hypochromic anemia with a red blood corpuscle count as low as 2 million per cubic millimeter and a hemoglobin reduced to as much as ✓30 per cent of normal. Calcium was determined in nine patients and showed a level of less than 9.0 mg. per 100 c.c. in five instances (averaging 8.5 mg.). No potassium determinations were carried out except in one patient (Case 27) where a value of 24 mg. per cent was obtained. Many of the chemical determinations were carried out long before death, and it can be presumed that more marked variations from the normal took place in many instances during the last days of life. This is especially true since several patients in our series showed a progressively increasing oliguria and often a terminal anuria.

PATHOLOGIC FINDINGS

The basic renal lesions are listed in Table II. There were four cases of arteriolonecrosis of the kidneys, two of them associated with arteriosclerosis, one with chronic glomerulonephritis, and one with chronic pyelonephritis.

The average weight of the heart was 466 grams, the minimum weight was 300 grams, and the maximum weight was 650 grams. There was no definite relation between the weight of the heart and the underlying renal disease. More consistently high weights, however, were found in nephrosclerosis of the arteriolar

TABLE

CASE	SEX AGE	CLINICAL INFORMATION	LABORATORY DATA	RENAL PATHOLOGY	HEART			PERICARDIUM	MYOCARDIUM AND ENDOCARDIUM	COR- ONARY AR- TERIO- SCLER- OSIS
					WT. (GM.)	R.V.W. (CM.)	L.V.W. (CM.)			
1	M 52	Enlarged prostate; cystotomy; phlebitis; angina pectoris; acute suppurative cystitis	Hb., —; R.B.C., —; N.P.N., 108; B.P., 136/92	Acute pyelonephritis with abscesses	350	0.4	1.2	Normal	Slight hypertrophy and fibrosis; old and organizing infarcts (I.V. septum); fat infiltration of right ventricle	+
2	M 56	Chronic glomerulonephritis; hypertensive heart disease; acute bronchopneumonia	Hb., 75%; R.B.C., 3.79; N.P.N., 86; B.P., 150/120	Nephrosclerosis of the arteriolar variety	525	0.4	1.3	Normal	Hypertrophy; moderate interstitial fibrosis; dilatation of chambers with mural thrombi	+
3	M 57	Chronic pyelonephritis and nephrolithiasis; hypertensive heart disease with failure	Hb., 55%; R.B.C., 2.3; N.P.N., 240; B.P., 180/90; Ca, 6.1	Pyelonephritic contracted kidneys; nephrolithiasis	500	0.4	1.6	Acute serofibrinous pericarditis with extension into the myocardium	Moderate hypertrophy; severe interstitial fibrosis, more marked in the outer third of the ventricular wall; slight endocardial fibrosis	+++
4	M 46	Hypertensive cardiorenal disease; acute bronchopneumonia	Hb., 50%; R.B.C., 3.33; N.P.N., >74; B.P., 220/110	Arteriosclerosis and necrosis	500	0.6	1.8	Acute fibrinous pericarditis with extension into the myocardium	Slight hypertrophy and fibrosis	++
5	M 62	Hypertensive cardiorenal disease; acute bronchopneumonia; pulmonary infarcts; prostatism	Hb., 70%; R.B.C., 3.95; N.P.N., 92; B.P., 184/130	Pyelonephritic contracted kidneys	650	0.7	2.0	Normal	Marked hypertrophy and interstitial fibrosis; old and recent infarcts of the anterior and posterior walls of the left ventricle and of the posterior wall of the right ventricle	+++

Coronary arteriosclerosis: +, slight; ++, moderate; +++, severe, with or without occlusion.

R.V.W.: Thickness of right ventricular wall.

L.V.W.: Thickness of left ventricular wall.

I.V. block: Intraventricular block.

NUM- BER OF ECG'S	FIRST ECG	LAST ECG	DEATH	ELECTROCARDIOGRAPHIC DIAGNOSIS							ECG AND NECROPSY AGREEMENT	FIG.
				HYPO- CAL- CEMIA	HYPER- POTAS- SEMIA	CHRONIC LEFT VENTRI- CULAR STRAIN	MYO- CARDIAL INFARCT	PERI- CARDI- TIS	NON- SPE- CIFIC ABNOR- MALITY	NOTE		
1	10/8/37		10/23/37	—	—		+	—		I.V. block (S type)	No dis- crepancy	
3	1/22/38	2/2/38	2/2/38	+	—			+			No pericar- ditis at autopsy	
2	9/8/38	10/17/38	10/19/38	+	—			?	+	I.V. block (Indeter- minate)	No dis- crepancy	
1	9/2/39		9/4/39	—	—		—	—	+	I.V. block (Indeter- minate)	Pericarditis at autopsy	
5	3/22/40	5/20/40	6/14/40	—	—		—	—	+	I.V. block (Common type)	Old (and recent) infarct at autopsy	

TABLE I

CASE	SEX AGE	CLINICAL INFORMATION	LABORATORY DATA	RENAL PATHOLOGY	HEART			PERICARDIUM	MYOCARDIUM AND ENDOCARDIUM	COR- ONARY AR- TERIO- SCLER- OSIS
					WT. (GM.)	R.V.W. (CM.)	L.V.W. (CM.)			
6	M 69	Prostatectomy; postoperative progressive acute uremia; broncho- pneumonia	Hb., 40%; R.B.C., 2.3; N.P.N., 110; B.P., 152/72	Acute pyc- lonephritis with abscesses	—	0.3	1.0	Old fibro- adhesive and recent sero- hemorrhagic pericarditis with exten- sion into the myo- cardium	Slight inter- stitial and perivascular fibrosis	+
7	F 57	Hypertensive heart disease with failure; marked oli- guria; acute broncho- pneumonia	Hb., 30%; R.B.C., 2.5; N.P.N., 98; B.P., 220/40	Pyelonephritic contracted kidneys with nephro- sclerosis	460	0.5	1.5	Petechial hemorrhages over right auricle	Moderate hyper- trophy and slight fibrosis	++
8	F 50	Chronic glomerulo- nephritis; oliguria; anuria during last 24 hours; acute broncho- pneumonia	Hb., 30%; R.B.C., 2.46; N.P.N., 144; B.P., 135/90	Pyelo- nephritic contracted kidneys	300	0.2	1.1	Normal	Slight hyper- trophy; mod- erate inter- stitial fibrosis	+
9	M 34	Hypertensive heart disease; pulmonary edema	Hb., 50%; R.B.C., 2.28; N.P.N., 124; B.P., 190/120; Ca, 9.6	Subchronic glomerulo- nephritis; arterial nephro- sclerosis	475	0.5	1.5	Normal	Marked hyper- trophy; inter- stitial and perivascular fibrosis; old anterior wall infarct with aneurysmal dilatation	+++
10	M 49	Malignant nephro- sclerosis; urea frost; syphilitic aortitis; acute broncho- pneumonia	Hb., 70%; R.B.C., 4.5; N.P.N., 152; B.P., 260/114; Ca, 10	Arteriolo- sclerosis and necrosis of the kidneys; acute pyelo- nephritis	500	0.6	2.5	Acute sero- fibrinous pericarditis with exten- sion into the myocardium	Marked hyper- trophy, mod- erate inter- stitial and perivascular fibrosis	++
11	M 63	Malignant nephro- sclerosis; hyperten- sive heart disease; acute broncho- pneumonia	Hb., —; R.B.C., —; N.P.N., 120; B.P., 196/106	Chronic pyelo- nephritis	650	0.3	1.7	Acute fibrinous pericarditis; old ad- hesions	Moderate hypertrophy; slight inter- stitial fibrosis; old infarct of the left ventricle (apex)	+++

CONT'D

NUMBER OF ECG'S	FIRST ECG	LAST ECG	DEATH	ELECTROCARDIOGRAPHIC DIAGNOSIS							ECG AND NECROPSY AGREEMENT	FIG.
				HYPO- CAL- CEMIA	HYPER- POTAS- SEMIA	CHRONIC LEFT VENTRI- CULAR STRAIN	MYO- CARDIAL INFARCT	PERI- CARDI- TIS	NON- SPE- CIFIC ABNOR- MALITY	NOTE		
3	7/13/40	7/23/40	7/23/40	—	—	—	—	—	+		Pericarditis at autopsy	
1	9/27/40		10/16/40	+	+	+	—	—			No dis- crepancy	
1	10/21/40		10/30/40	++	—	—	—	—	+		No dis- crepancy	
1	10/22/40		11/15/40	—	—		+	—			No dis- crepancy	
2	10/10/40	11/15/40	11/18/40	+	—		—	+		Left ven- tricular strain obscured by peri- carditis	No dis- crepancy	1
9	9/30/40	4/12/41	5/2/41	—	—	?	?	—	+	Combined heart strain ?	No dis- crepancy	

TABLE I

CASE	SEX AGE	CLINICAL INFORMATION	LABORATORY DATA	RENAL PATHOLOGY	HEART			PERICARDIUM	MYOCARDIUM AND ENDOCARDIUM	COR- ONARY AR- TERIO- SCLER- OSIS
					WT. (GM.)	R.V.W. (CM.)	L.V.W. (CM.)			
12	M 79	Hypertrophy of the prostate; ascending pyelonephri- tis; acute broncho- pneumonia	Hb., 50%; R.B.C., 2.9; N.P.N., 157; B.P., 150/100	Chronic pyelo- nephritis	450	0.2	1.2	Normal	Slight hyper- trophy	+
13	F 15	Hydro- nephrosis with malignant hypertension and heart failure	Hb., 40%; R.B.C., 1.8; N.P.N., 118; B.P., 230/160	Chronic pyelo- nephritis with bi- lateral hydro- nephrosis; arteriolo- necrosis	400	0.4	1.2	Normal	Moderate hyper- trophy; slight interstitial and peri- vascular fibrosis	0
14	M 65	Nephro- sclerosis with hyper- tensive heart disease; acute broncho- pneumonia	Hb., 87%; R.B.C., 4.67; N.P.N., 118; B.P., 180/98; Ca, 11.0	Arteriolo- sclerosis; acute glomerulo- nephritis	425	0.4	1.5	Normal	Moderate hyper- trophy; slight interstitial and perivascular fibrosis; acute myocarditis	+
15	F 55	Old nephrec- tomy; chronic renal disease with heart failure	Hb., 49%; R.B.C., 3.2; N.P.N., 152; B.P., 160/88	Chronic pyelo- nephritis	400	0.4	1.2	Normal	Moderate hyper- trophy and interstitial fibrosis; old and recent in- farcts of the left ventricle (apex)	+++
16	M 26	Chronic glomerulo- nephritis; hypertensive heart disease with failure	Hb., 36%; R.B.C., 2.0; N.P.N., 154; B.P., 200/130; Ca, 8.1	Chronic pyelo- nephritis; proliferative glomerulo- nephritis	400	0.4	1.3	Acute peri- carditis (partial)	Slight hyper- trophy; slight interstitial and peri- vascular fibrosis	++
17	F 42	Chronic glomerulo- nephritis; hypertensive heart disease with failure; pulmonary edema	Hb., 43%; R.B.C., 2.50; N.P.N., 171; B.P., 195/110	Chronic glomerulo- nephritis	425	0.3	1.0	Acute fibrinous pericarditis with ex- tension into the myocardium	Moderate hyper- trophy and interstitial fibrosis; fat infiltration of right ventricle	++

CONT'D

NUM- BER OF ECG'S	FIRST ECG	LAST ECG	DEATH	ELECTROCARDIOGRAPHIC DIAGNOSIS							EGG AND NECROPSY AGREEMENT	FIG.
				HYPO- CAL- CEMIA	HYPER- POTAS- SEMIA	CHRONIC LEFT VENTRI- CULAR STRAIN	MYO- CARDIAL INFARCT	PERI- CARDI- TIS	NON- SPE- CIFIC ABNOR- MALITY	NOTE		
1	4/12/41		5/22/41	—	—	+	—	—			No dis- crepancy	
5	5/20/40	10/13/41	12/1/41	+	++	+	—	—			No dis- crepancy	
1	4/15/42		4/20/42	—	—	+	—	—			No dis- crepancy	
1	6/16/42		7/8/42	—	—	+	—	—			Old (and recent) infarct at autopsy	
1	7/10/42		8/6/42	++	—	?	—	?	+	Combined heart strain ?	No dis- crepancy	
5	6/15/38	8/8/42	8/13/42	++	++		—	?		Left ven- tricular strain obscured by K changes	No dis- crepancy	2

TABLE I

CASE	SEX AGE	CLINICAL INFORMATION	LABORATORY DATA	RENAL PATHOLOGY	HEART			PERICARDIUM	MYOCARDIUM AND ENDOCARDIUM	COR- ONARY AR- TERIO- SCLER- OSIS
					WT. (GM.)	R.V.W. (CM.)	L.V.W. (CM.)			
18	M 50	Arterio- sclerotic heart dis- ease with uremia; urea frost; oliguria; acute broncho- pneumonia	Hb., 54%; R.B.C., 3.88; N.P.N., 120; B.P., 260/150; Ca, 9.5	Old pyelo- nephritis; arteriolo- sclerosis of the kidneys	500	0.4	1.6	Normal	Moderate inter- stitial and perivascular fibrosis, especially marked in the outer third; moderate hypertrophy	++
19	F 24	Tuberculous osteo- myelitis; pregnancy; chronic glomerulo- nephritis with uremia and terminal anuria	Hb., 45%; R.B.C., 3.26; N.P.N., 224; B.P., 220/158; Ca, 7.8	Amyloidotic contracted kidneys	475	0.4	2.1	Acute and organizing fibrino- hemorrhagic pericarditis	Moderate hyper- trophy; moderate interstitial and perivascular fibrosis	+
20	F 44	Malignant nephro- sclerosis; uremia; pro- gressive oliguria; acute broncho- pneumonia	Hb., 60%; R.B.C., 3.38; N.P.N., 155; B.P., 210/140	Subacute glomerulo- nephritis and arteriolo- necrosis	400	—	—	Acute fibrinous pericarditis	Moderate fibrosis and hypertrophy	++
21	M 28	Hypertensive cardiorenal disease with oliguria; multiple pulmonary infarcts	Hb., 54%; R.B.C., 2.49; N.P.N., 100; B.P., 210/35	Subacute glomerulo- nephritis and arteriolo- necrosis	500	0.3	1.8	Minimal lymphocytic infiltration	Moderate to severe hyper- trophy and fi- brosis; some fatty degenera- tion; mural thrombi in right auricle	++
22	M 58	Hypertensive cardio- vascular dis- ease; hydro- thorax	Hb., 60%; R.B.C., 3.60; N.P.N., 112; B.P., 210/140	Polycystic kidneys	475	0.7	1.9	Normal	Moderate hyper- trophy and fibrosis; old infarct of anterior wall of left ventricle and inter- ventricular septum; moderate endocardial thickening	+++

CONT'D

NUM- BER OF ECG'S	FIRST ECG	LAST ECG	DEATH	ELECTROCARDIOGRAPHIC DIAGNOSIS							EGG AND NECROPSY AGREEMENT	FIG.
				HYPO- CAL- CEMIA	HYPER- POTAS- SEMIA	CHRONIC LEFT VENTRI- CULAR STRAIN	MYO- CARDIAL INFARCT	PERI- CARDI- TIS	NON- SPE- CIFIC ABNOR- MALITY	NOTE		
1	8/13/42		8/24/42	—	—	+	—	—			No dis- crepancy	
5	2/11/42	11/3/42	11/4/42	+	—	+	—	+			No dis- crepancy	
2	12/17/42	5/14/43	5/28/43	++	—	+	—	—		Combined heart strain	No dis- crepancy	
1	6/28/43		8/25/43	++	—	+	—	—		Combined heart strain	No dis- crepancy	
17	6/21/33	7/30/43	9/21/43	—	—	?	+	—		Combined heart strain?	No dis- crepancy	

TABLE I

CASE	SEX AGE	CLINICAL INFORMATION	LABORATORY DATA	RENAL PATHOLOGY	HEART			PERICARDIUM	MYOCARDIUM AND ENDOCARDIUM	COR- ONARY AR- TERIO- SCLER- OSIS
					WT. (GM.)	R.V.W. (CM.)	L.V.W. (CM.)			
23	F 52	Hypertensive heart disease; nephrosclerosis; uremia	Hb., 52%; R.B.C., 3.05; N.P.N., 94; B.P., 220/120	Nephrosclerosis of the arteriolar variety	550	0.4	1.8	Normal	Severe diffuse fibrosis and hypertrophy; multiple small infarcts of right and left ventricles	+++
24	F 22	Chronic glomerulonephritis with moderate oliguria and uremia; severe anemia	Hb., 25%; R.B.C., 1.60; N.P.N., 300; B.P., 175/135	Subchronic glomerulonephritis	375	0.3	1.8	Normal	Slight interstitial fibrosis and hypertrophy; moderate fatty degeneration; fat infiltration of the right ventricle	++
25	M 28	Chronic glomerulonephritis; hypertension; acute bronchopneumonia	Hb., 53%; R.B.C., 3.89; N.P.N., 125; B.P., 180/100; Ca, 8.8	Acute pyelonephritis superimposed on chronic pyelonephritic contracted kidneys	525	0.5	1.8	Acute fibrinous pericarditis	Moderate hypertrophy; slight interstitial fibrosis; severe cloudy swelling; acute endocarditis of mitral valve	+
26	M 62	Nephrolithiasis; chronic pyelonephritis; marked oliguria with terminal anuria; acute bronchopneumonia	Hb., 43%; R.B.C., 2.50; N.P.N., 116; B.P., 160/110	Pyelonephritic contraction of left kidney; compensatory hypertrophy and arteriosclerosis of right kidney	400	0.5	1.5	Acute serofibrinous hemorrhagic pericarditis	Moderate hypertrophy and interstitial fibrosis	++
27	M 51	Hypertensive heart disease; diabetes mellitus; intracapillary glomerulosclerosis	Hb., 39%; R.B.C., 2.1; N.P.N., 200; B.P., 200/100; Ca, 6.2; K, 24	Pyelonephritic contracted kidneys	600	0.8	2.3	Organized fibro-adhesive pericarditis; few small hemorrhages	Marked hypertrophy; moderate interstitial fibrosis; some cloudy swelling; moderate sclerotic thickening of mitral and aortic valves	++

CONT'D

NUMBER OF ECG'S	FIRST ECG	LAST ECG	DEATH	ELECTROCARDIOGRAPHIC DIAGNOSIS							EGG AND NECROPSY AGREEMENT	FIG.
				HYPO-CAL-CEMIA	HYPER-POTAS-SEMIA	CHRONIC LEFT VENTRI-CULAR STRAIN	MYO-CARDIAL INFARCT	PERI-CARDI-TIS	NON-SPE-CIFIC ABNOR-MALITY	NOTE		
1	9/27/43		9/27/43	—	—	+	—	—			Small in-farcts at autopsy	
1	10/13/43		10/24/43	++	+		—	—			No dis-crepancy	
8	7/10/29	11/26/43	12/8/43	+	+	+	—	—			No dis-crepancy	
3	3/21/44	4/24/44	4/24/44	—	++		—	—		Left ven-tricular strain obscured by K changes; I.V. block (S type); A-V block	No dis-crepancy	4
7	4/6/42	9/2/45	9/8/45	++	+	+	—	—			No dis-crepancy	3

TABLE II

Acute ascending pyelonephritis	2
Chronic pyelonephritis	13
Subacute and chronic glomerulonephritis	5
Nephrosclerosis of the arteriolar variety	5
Amyloid contracted kidneys	1
Polycystic kidneys	1

variety, while approximately normal weights were present in two instances of acute ascending pyelonephritis. Both ventricles were proportionally equally affected by the hypertrophic process. Acute diffuse fibrinous pericarditis was present in eleven (41 per cent) instances. The average nonprotein nitrogen level in these patients was slightly higher (149 mg. per 100 c.c.) than in the others, but no definite relationship could be established between these two findings. Often urea frost on the skin was seen in patients who did not present pericarditis. The pericarditis was generally recent, evidence of an early organization being present in three instances. In six hearts there was a definite extension of the inflammatory process from the pericardium into the superficial layers of the myocardium. However, it is possible that a larger number of sections would have shown involvement of the myocardium in a higher percentage of cases (Fig. 5). The only instance of diffuse myocarditis in our series was not associated with pericarditis and probably was the consequence of an acute bronchopneumonia. In most cases of pericarditis, degeneration of the muscle fibers was more marked in the superficial than in the deeper layers of the myocardium. When pericarditis was absent, this localization of the major degenerative changes could not be observed.

The myocardium was generally rather pale with a moderate to severe cloudy swelling. The consistency was diminished in only a few instances and occasionally edema was present. Old and recent myocardial infarcts were observed in seven hearts, most frequently in the anterior wall of the left ventricle. Microscopically, the most consistent finding in the myocardium was a moderate to severe interstitial fibrosis which was present in the hearts of all but two patients. Both of these patients had acute uremia. In a few instances the myocardial fibrosis was particularly marked in perivascular location. In others either the outer or the inner third of the left ventricular wall was more severely involved. A diffuse, slight fatty degeneration was noted in many hearts. In only two instances, however, did it reach a severe degree; both of these patients had a marked anemia. Fat infiltration of the right ventricular wall was present in eight hearts; the infiltration was rather marked in three.

The mural and valvular endocardium was essentially normal. Occasionally mural thrombi, subendocardial hemorrhages, and endocardial thickening were found. The coronary arteries presented a moderate to severe arteriosclerosis in all cases. This was particularly true in the extramural branches, while the intramural arteries, as a rule, presented less severe changes. In all instances of renal arteriolosclerosis and arteriolonecrosis, similar changes in the heart were

carefully looked for. We were unable to find necrosis of the myocardial arterioles in any of the four instances in which such change occurred in the kidney. Arteriosclerosis was frequently present although never in the same degree as in the kidney. Endothelial hyperplasia of the small arteries was also noted in a few instances.

ELECTROCARDIOGRAPHIC FINDINGS

Left Heart Strain.—Evidence of left heart strain in the last electrocardiogram was present in twelve patients; in three other patients the diagnosis had been made in a previous record but was obscured in the last record by changes produced by

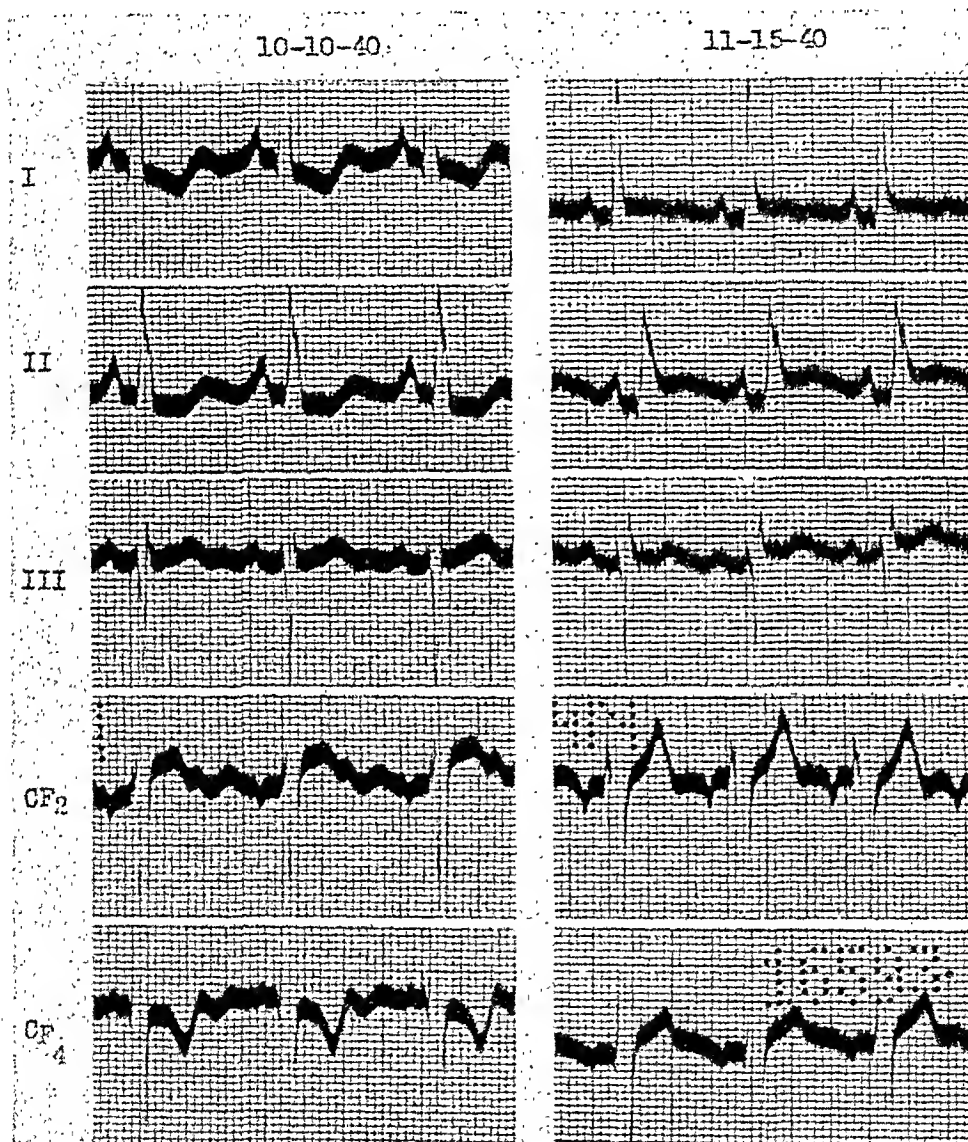


Fig. 1.—Case 10. The record taken Oct. 10, 1940, is characteristic of chronic left heart strain. The typical S-T depression in Leads I and II is replaced by an S-T elevation in the tracing made Nov. 15, 1940; this is ascribed to the effect of acute diffuse pericarditis.

hyperpotassemia (Figs. 2 and 4 and Table I, Cases 17 and 26) or by pericarditis (Fig. 1, Case 10). Of the remaining twelve patients, seven showed changes in all available records which may have masked the pattern of left heart strain. The

8-8-42

5-8-42

6-15-38

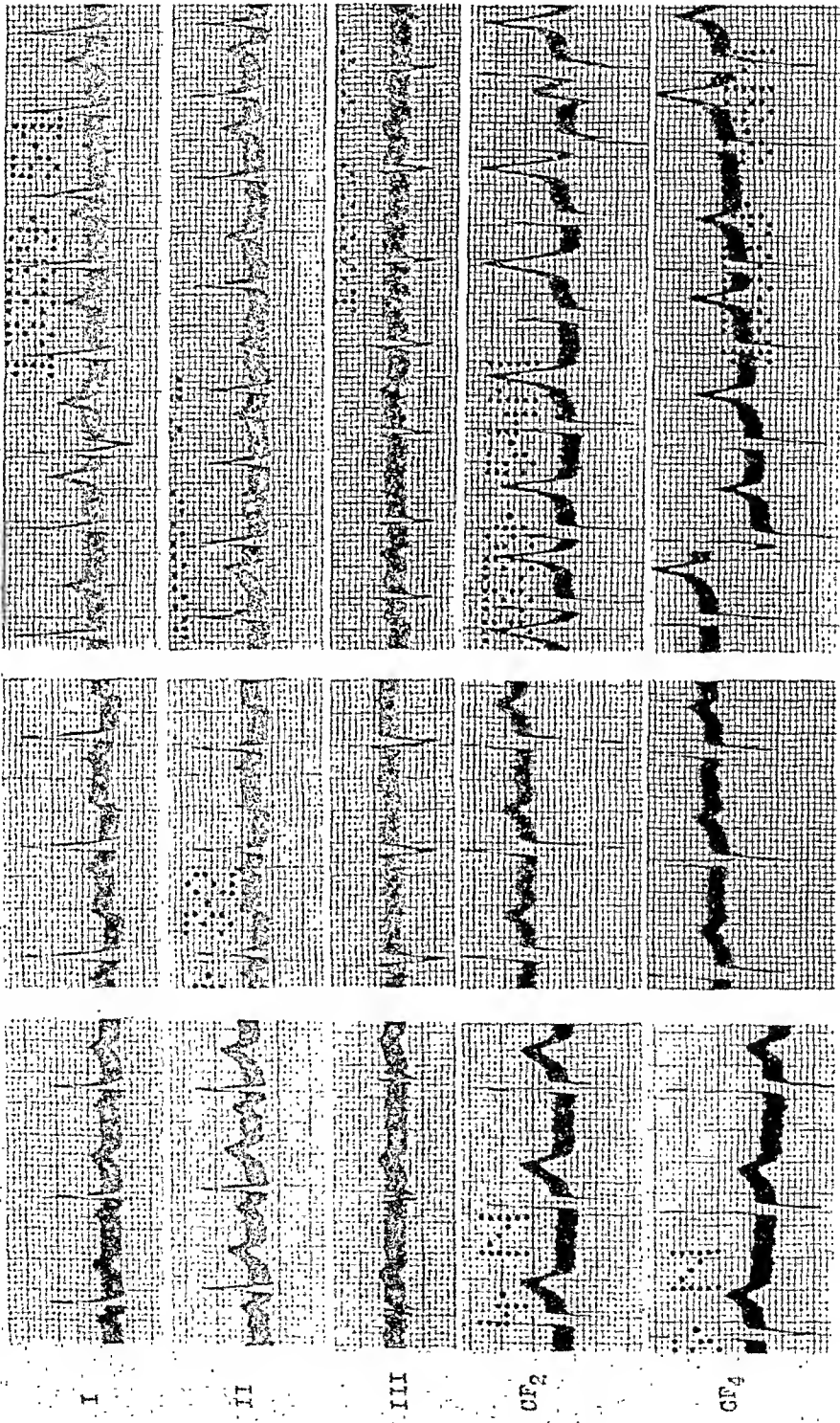


Fig. 2.—Case 17. A normal left axis shift (June 15, 1938) is changed to the pattern of chronic left heart strain (May 9, 1942) and, finally, when uremia develops (Aug. 8, 1942), changes due to hypocalcemia (prolonged electrical systole) and to hyperpotassemia (tall and narrow T waves) appear: sinus rhythm is replaced by auricular fibrillation. Note how the potassium changes obscure the pattern of left heart strain. There are premature ventricular systoles in the last record.

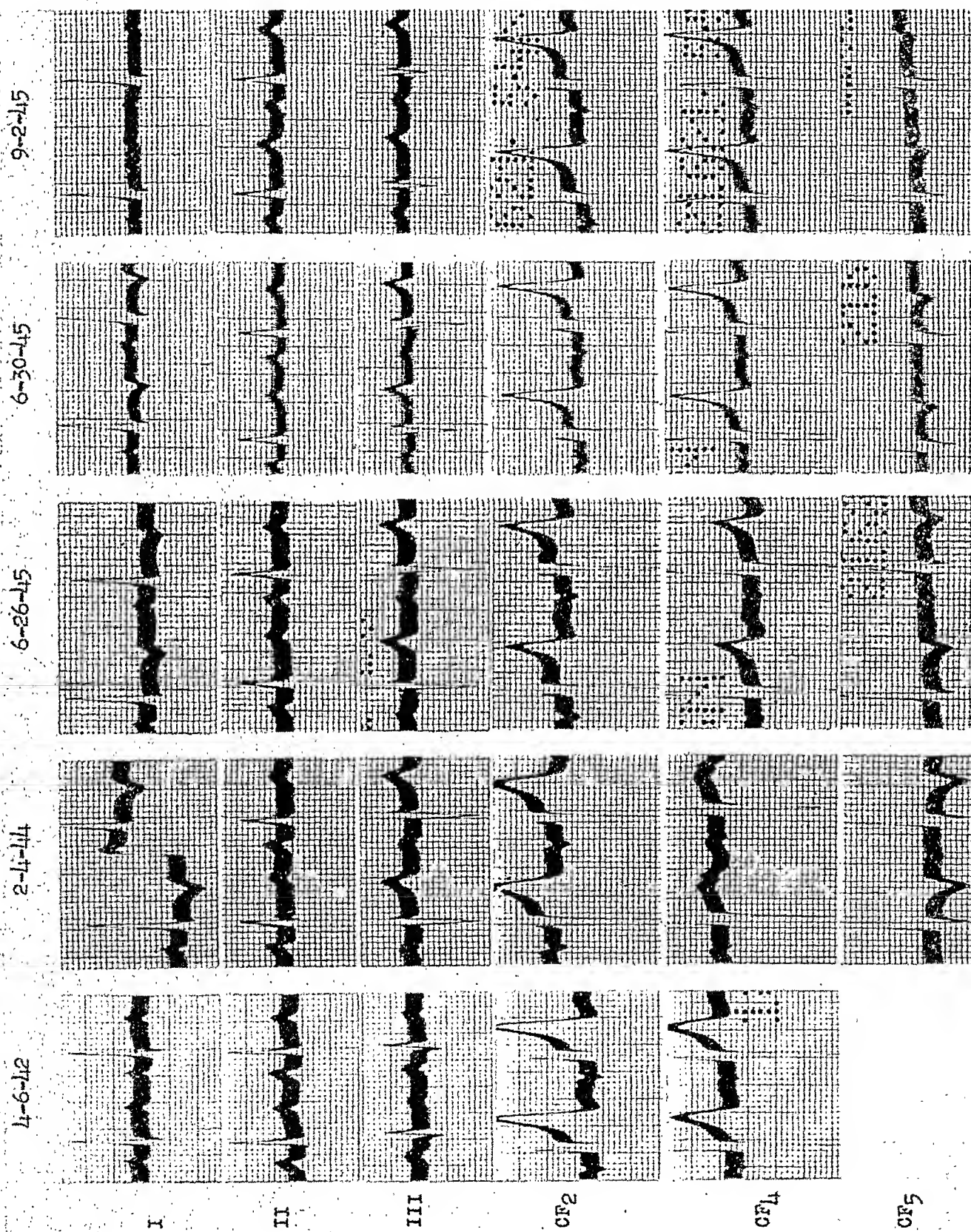


Fig. 3.—Case 27. Note the development of the pattern of left heart strain (Feb. 4, 1944), the evidence of hypocalcemia (prolonged electrical systole) (June 26, 1945), and, finally (June 30, 1945), the appearance of the tall and narrow T wave indicative of hyperpotassemia. Note the potassium effect on the inverted T of left heart strain in Leads I and CF₅ (Sept. 2, 1945).

masking changes consisted of a myocardial infarction pattern in two instances, a pericarditis pattern in one, and intraventricular block in four. In the remaining five cases, nonspecific S-T and T-wave changes were present; in two of this last group the possibility of combined right and left ventricular strain^{1,2} was con-

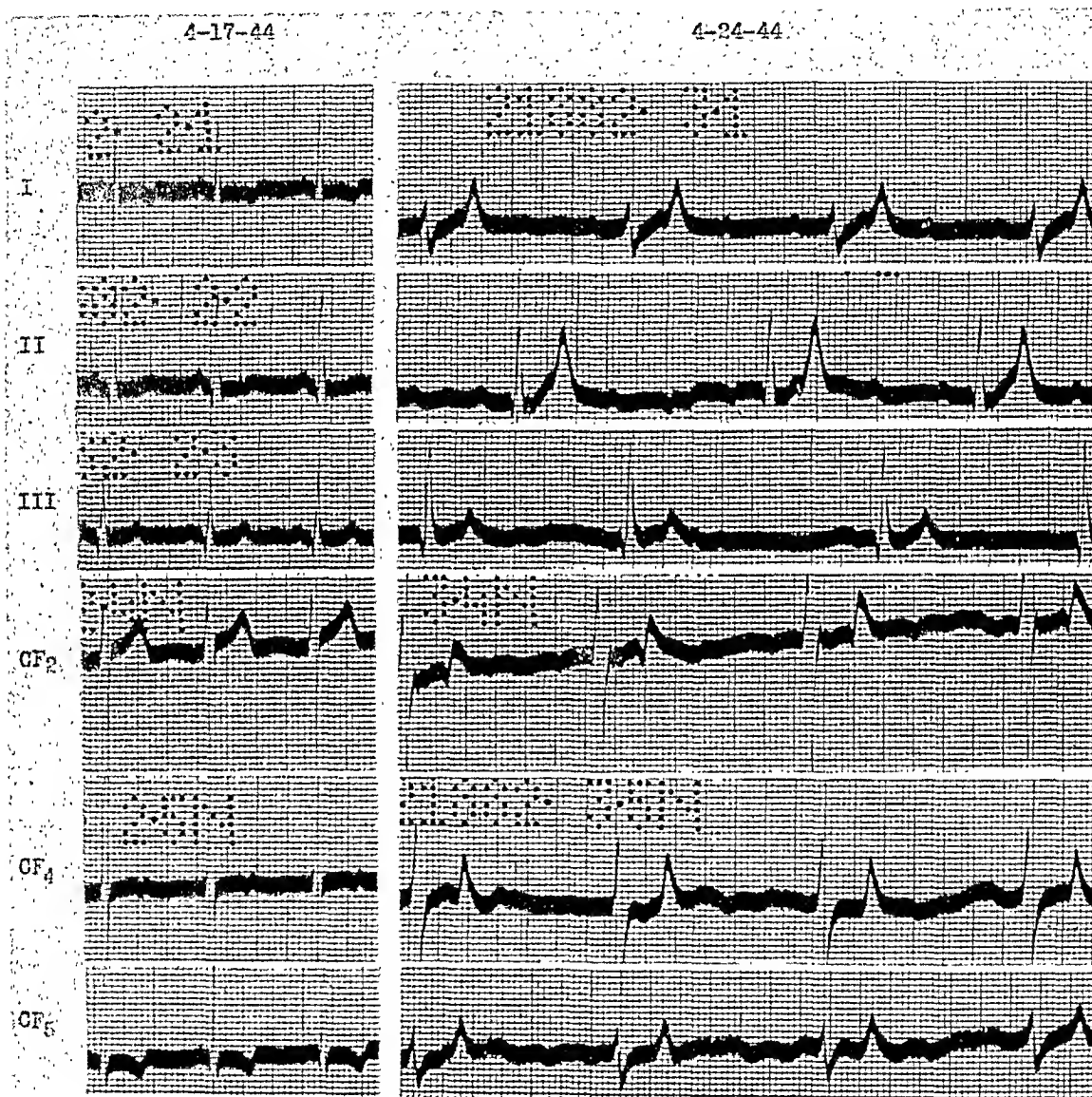


Fig. 4.—Case 26. Effect of uremia on the pattern of "concordant" left heart strain (April 17, 1944). A record taken less than twenty-four hours before death (April 24, 1944) shows second degree A-V block (varying between 4:1 and 3:1), intraventricular block, and tall and narrow T waves.

sidered. In the entire group there was no discrepancy between the electrocardiographic findings and the findings at autopsy, inasmuch as there was no instance where hypertrophy was diagnosed and not found at autopsy and no instance of hypertrophy found post mortem where one of the factors just mentioned did not explain the lack of evidence in the electrocardiogram. Nevertheless,

if chest lead CF₅ had been available in all cases, our accuracy in diagnosing left heart strain might have been enhanced.

Myocardial Infarction.—Myocardial infarction was diagnosed in three patients. In two, this lesion was interpreted as being a recent one; in one patient an old lesion was suspected and confirmed by necropsy. Autopsy revealed old myocardial infarcts in three additional patients, two of whom also showed recent infarcts which occurred after the last electrocardiogram had been obtained.

Pericarditis.—Pericarditis with spread to the adjacent myocardium was correctly diagnosed in two patients and suspected and confirmed by autopsy in three other patients. In two additional patients acute pericarditis with spread to the myocardium found post mortem was not reflected in the electrocardiogram. Finally, in one instance T-wave inversions in all limb leads led to the diagnosis of subacute pericarditis which was not confirmed by autopsy.

Hypocalcemia.—The duration of the electrical systole³ was measured and compared with the value obtained according to the formula $S = 0.39\sqrt{C} \pm 0.04$ second.^{3,b} As pointed out by Hegglin and Holzman,^{3,b} prolongation of the electrical systole due to hypocalcemia is characterized by prolongation of the S-T segment without broadening of T; this becomes even more obvious when T is abnormally narrow as a result of hyperpotassemia. The electrical systole was prolonged in fourteen patients, in seven of them exceeding the upper limit of the expected value by 0.01 to 0.04 second (listed as + in Table I), and in seven patients, by 0.05 to 0.11 second (listed as ++ in Table I). Such prolongation of the electrical systole was observed in records taken two and one-half years to one day before death. In all but one patient (Case 10) in whom the serum calcium level was determined, the diagnosis of hypocalcemia (less than 10 mg. per cent) was confirmed.

Hyperpotassemia.—Changes ascribed to hyperpotassemia were observed in seven patients. They consisted of changes in T-wave contour in six cases and, in addition, A-V and intraventricular block in one case. The changes are identical with those reported in the literature in experimental potassium poisoning and hyperpotassemia in man which will be reviewed later. The T-wave changes were always of a concordant type, T becoming tall and narrow in the three limb leads and also in the chest leads. In several such instances, previous records were available and showed the profound alteration of an abnormal pre-existing pattern as a result of potassium poisoning (Figs. 2, 3, and 4 and Cases 17, 26, and 27 in Table I); thus, the inverted T of chronic left heart strain was gradually replaced by the upright potassium T wave (Fig. 2, Case 17). The potassium changes were found chiefly in patients with severe oliguria; however, in two patients (Cases 13 and 27) they were observed as early as six and nine weeks before death. T-wave changes characteristic of potassium poisoning were associated with prolongation of the electrical systole in all but one instance (Case 26), and the latter change was found to precede the potassium changes in all instances where earlier records were available. Determination of the serum potassium was

available only in Case 27, but the conditions of the occurrence of the characteristic electrocardiographic changes and their identical appearance with findings reported in established hyperpotassemia justify our interpretation.

Nonspecific Abnormalities.—Nonspecific abnormalities were present in four patients; in two instances in records taken three weeks before death, in the others in records taken two days and one day before death. Three other cases with nonspecific contour changes showed a prolonged electrical systole characteristic of hypocalcemia.

DISCUSSION

Pathologic Findings.—While the pathologic changes in the pericardium in uremia have been well known for a long time, there are only a few reports concerning changes in the myocardium. Bright and others recognized the existence of such changes, but their real nature was not further investigated until recently in connection with electrocardiographic observations.

Lüscher^{4a} described a severe hemorrhagic myocarditis associated with fibrinous pericarditis in a patient with typical uremia. He believed that there was a uremic myocarditis. Richter and O'Hare,^{4b} in analyzing the cardiac findings in chronic glomerulonephritis and especially in uremia, concluded that the heart in this condition is essentially the same as in primary vascular hypertension except for the modification brought about by the lower average age, by the duration of the hypertensive process, by the degree of hypertension, and by the terminal uremic pericarditis. Pericarditis was present in 48 per cent of their series, while the myocardial changes were considered unimportant and non-typical. Gouley,^{4c} on analyzing the hearts of thirty-four patients with uremia, noted a flesh-colored mottling of the muscle with foci of yellowish-gray myocardial degeneration most frequently located in the subepicardial layer of the myocardium. Histologically the main changes observed were fatty and hyaline degeneration with marked swelling of the myocardial fibers; little or no cellular infiltration was found. The fatty degeneration was more marked in the subepicardial layers. Pericarditis was present in 22 per cent of the cases, and since it was not seen in the absence of myocardial degeneration, it was considered to be secondary to the myocardial changes. While rejecting the term uremic myocarditis as improper, Gouley believes in the existence of a specific uremic myocardiopathy. Saphir^{4d} found only five of 240 cases of myocarditis associated with acute or chronic glomerulonephritis or uremia per se. He did not consider the myocardial changes typical for uremia but considered them to be similar to the changes found in any wasting or chronic infectious disease. The vascular changes were similar to those observed in the kidneys in arteriosclerosis and arterionecrosis. Solomon and associates^{4e} were unable to demonstrate any lesion characteristic of the uremic state in the hearts of fifty patients who died in uremia. An unusual endothelial hyperplasia of the cardiac arterioles was present in seven of eight patients with acute necrotizing arteriolitis of the kidneys, but in no other type of renal pathology was there any correlation with the cardiac changes. Other microscopic changes observed were a diffuse fatty degeneration,

miliary myocardial necrosis; acute interstitial myocarditis (thirty-one cases), and acute miliary infarctions. Either acute or chronic pericarditis was present in 36 per cent of their cases. Winternitz and co-workers^{4,f} described anatomic changes in the heart following experimental ligation of both renal arteries in the dog. Edema, hemorrhages, and necroses were noted both in the myocardium and in the small branches of the coronary arteries. However, the production of acute uremia in animals is not comparable with the condition in man where the uremic process progresses slowly over a period of months.

Analysis of the pathologic findings in our series confirms the generally accepted view that if pericarditis is excluded, there are no demonstrable characteristic anatomic changes of the heart in uremia. The hypertrophy of the heart and the interstitial fibrosis of the myocardium are evidently due to the arterial hypertension and to the associated arteriosclerotic process, respectively. The relative rarity of a severe sclerotic process in the intramural coronary arterioles may be due to the fact that the extravascular support of the myocardium acts to protect the smaller intramural arteries from the injurious effect of the elevated arterial blood pressure. Endothelial hyperplasia of the small arteries was neither as frequent nor as typical as reported by Solomon, Roberts, and Lisa.^{4,g} Pericarditis frequently extended into the superficial layers of the myocardium and this is important in relation to the electrocardiographic changes. The fatty degeneration of the myocardial fibers, often severe, is certainly not specific. This degeneration, when present, is most likely due to the severe anemia exhibited by these patients. We were unable to confirm the findings of Gouley concerning the subepicardial localization of the degenerative changes.

The severe cloudy swelling and the occasional edema of the myocardium can, of course, be considered to be due to the profoundly altered physiochemical changes and to the modification of the electrolyte balance known to occur in the tissues in uremia. Certain metabolites known to increase in the serum have been demonstrated to be present in increased amounts in the heart muscle.⁵

The changes of the calcium and potassium contents of the blood must be emphasized. They have a direct effect on the myocardial fiber and determine typical changes in the electrocardiogram. In uremia, especially when it is the result of chronic glomerulonephritis, there is a diminution of the calcium content in the blood (hypocalcemia) because of retention of phosphates.⁶ The increase of potassium in body fluids (hyperpotassemia) which occurs in uremia results from the breakdown of body cells and the inability on the part of the body to excrete the potassium by any channel other than the kidney or to store any considerable amount.⁷

In marked experimental hyperpotassemia produced in dogs, Hall and Cleg-horn⁸ demonstrated changes in the heart which consisted grossly of petechial hemorrhages and microscopically of changes in the small and medium-sized arteries. These showed desquamation of endothelial cells, occasional thrombosis with occasional organization, degeneration of the media, and edema of the arterial wall. In a few instances in our series where the electrocardiogram showed evidence of hyperpotassemia, a careful search revealed no lesions attributable to retained potassium. This is in accordance with the findings of Keith and co-workers.⁹



B.

A.

Fig. 5.—Two cases of uremic pericarditis. Sections through the outer layer of the ventricular wall. A, Pericarditis limited to the epicardium. Note the abundant fibrinous exudate and the lymphocytic and mononuclear infiltration of the subepicardial fat tissue. B, Pericarditis with extension into the myocardium. The inflammatory cells extend deeply into the myocardium.

Electrocardiographic Findings.—Of the various changes encountered in electrocardiograms taken in patients with uremia, primarily those ascribed to hyperpotassemia need further discussion. A brief review of the recent advances in this subject will clarify our problem.

In 1938 Winkler, Hoff, and Smith^{10,a} observed a characteristic sequence in the electrocardiogram of the dog after intravenous injection of potassium similar to that previously described by Wiggers^{10,b} and others. The same sequence of electrocardiographic changes was observed in 1940 by Winternitz and associates^{4,f} and in 1941 by Hoff, Smith, and Winkler⁷ in experimental anuria; the identification of the electrocardiographic alterations as those of potassium poisoning led to the assumption that hyperpotassemia was the cause of death in experimental anuria. This was confirmed by actual determinations of serum potassium. Undoubtedly the T-wave changes after bilateral ureteral ligation described previously by Nicholson and Schechter^{10,c} were also due to the rise in serum potassium. Before hyperpotassemia and its reflection in the electrocardiogram were observed in uremia in man, other conditions with a disturbed potassium metabolism were found to show a close relation between serum potassium level and electrocardiogram. This was described, on the one hand, by Thomson^{10,d} in a case of Addison's disease with varying serum potassium; on the other hand, by Stewart, Smith, and Milhorat^{10,e} in cases of familial periodic paralysis with abnormally low serum potassium during the attacks. Similarly, potassium given by mouth both to individuals without renal impairment and to patients with chronic nephritis^{10,f-i} led to transitory electrocardiographic changes characterized by an increase in voltage and decrease in duration of T; the inverted T₁ in cases with left heart strain became less inverted or diphasic and transitory intraventricular block was also observed. The opposite effect on the T wave (leading to lowering or inversion of the T waves) of desoxycorticosterone acetate by lowering of serum potassium was emphasized by Currens and White,^{10,j} who considered the electrocardiogram a valuable index in the course of treatment of Addison's disease. The same effect of desoxycorticosterone acetate on the electrocardiogram of normal individuals was observed by Raab.^{10,k}

✓In human uremia, abnormally tall T waves were first described by Wood and White^{11,a} in five of thirty-eight patients with uremia many years before their relation to the increase in serum potassium was known. Misske^{11,b} found tall peaked T waves which he ascribed to asphyxia in nine of fifty-three cases of uremia and regarded this change in the patient's electrocardiogram as a sign of the approaching death. Finch and Marchand^{11,c} recorded electrocardiograms during the terminal stage of two patients with renal insufficiency and fatal potassium poisoning who showed the terminal arrhythmias of potassium intoxication. Keith and co-workers⁹ observed the evolution of intraventricular block in three instances of uremia with hyperpotassemia. The intraventricular conduction disturbance appeared less than one week before death in two of their patients. Bywaters^{11,d} reported electrocardiographic changes characteristic of potassium poisoning in cases of crush syndrome with hyperpotassemia.

In our own series, five of twenty-five unselected cases of uremia exhibited electrocardiographic evidence of potassium poisoning. This is a rather high

incidence (20 per cent) and probably would have been even higher if more electrocardiograms had been taken in the terminal stage of the disease. It suggests, in contrast to previous reports, that the mode of death in an appreciable number of cases of uremia in man is cardiac standstill or ventricular fibrillation resulting from potassium poisoning of the heart muscle. Six of our patients showed the early sign of potassium poisoning, the characteristic change in T-wave contour without any abnormality of rhythm or disturbance of A-V or intraventricular conduction. The latter changes were present in one case in an electrocardiogram taken less than twenty-four hours before death.

As was mentioned before, the tall potassium T waves of our series, with a single exception, were always associated with a prolonged electrical systole indicative of hypocalcemia. This combination can be considered highly suggestive of uremia. However, prolongation of the electrical systole has been described in Addison's disease,¹² in which condition hyperpotassemia with characteristic T-wave changes can be observed; to our knowledge this is the only other clinical condition which may be responsible for this peculiar combination in the electrocardiogram otherwise diagnostic of uremia.

Disagreement between electrocardiographic interpretation and anatomic evidence represents a real discrepancy in six cases of our series (three cases of pericarditis and three cases of myocardial infarction, Table I). In other cases changes found at necropsy were not reflected in the electrocardiogram because they took place only after the last electrocardiogram had been recorded or because a combination of conditions having opposite effects on the electrocardiogram was present, so that the expected changes may have balanced each other; the latter is particularly true for the effects of chronic left heart strain and hyperpotassemia. It has been emphasized in a previous report correlating electrocardiographic and anatomic findings¹³ that old healed myocardial infarcts may no longer be recognizable in the electrocardiogram; this was confirmed in three patients of the present series. It has been shown¹⁴ that diffuse pericarditis does not lead to electrocardiographic changes unless there is a spread of the inflammatory process to the subjacent myocardium. This explains the absence of electrocardiographic evidence of pericarditis in most cases of our series. No instance was encountered showing a combination of pericarditis (concordant elevation of the S-T segments) with potassium changes (tall narrow T waves) which would allow a specific diagnosis of uremic pericarditis; however, a review of the reported cases of pericarditis disclosed one such instance published by Wood and White.^{11, 15} (Fig. 4)

SUMMARY

1. Twenty-seven fatal cases of uremia are presented and their electrocardiographic and anatomic changes are described.

2. The sole demonstrable characteristic anatomic lesion is pericarditis, which was present in 41 per cent of the series and which frequently extended into the adjacent myocardium.

3. The myocardial changes are those attributed to hypertensive heart disease with additional diffuse fatty degeneration, cloudy swelling of myocardial fibers, and interstitial edema. While the fatty degeneration was probably caused by concomitant anemia, the cloudy swelling and interstitial edema can be attributed to the uremic intoxication but cannot be considered diagnostic of uremia. There is no evidence to support the existence of a specific so-called uremic myocarditis.

4. The factors responsible for the changes in the electrocardiogram of patients with uremia are chronic left heart strain, myocardial changes due to coronary artery disease, diffuse pericarditis, and changes in the electrolyte balance which give rise to hypocalcemia and hyperpotassemia. Because of the opposite effect of some of these factors on the electrocardiogram, the changes tend to obscure or balance each other, as revealed by serial electrocardiograms.

5. Evidence of hyperpotassemia was found in six cases. Tall narrow T waves, which are the early sign of potassium poisoning, were seen in five cases; additional intraventricular and auriculoventricular conduction disturbances, a later sign of potassium poisoning, were present in one case. The terminal stages of potassium poisoning which are characterized by auricular standstill and final ventricular standstill or ventricular fibrillation were not observed, since no tracings were obtained immediately before death.

6. T-wave changes indicative of hyperpotassemia were observed in one case as long as nine weeks before death.

7. The effect of hyperpotassemia on the electrocardiographic pattern of left heart strain is emphasized.

8. The combination of a prolonged electrical systole of the hypocalcemic type with narrow tall T waves indicative of potassium poisoning is the most characteristic electrocardiographic feature of uremia.

9. Potassium poisoning seems to be the immediate cause of death in at least one-fifth of the cases of uremia in man; the electrocardiogram is of value for the diagnosis of hyperpotassemia and thus may give a hint as to the immediate prognosis in patients with uremia.

The authors wish to acknowledge their appreciation of the valuable suggestions of Dr. L. N. Katz and Dr. O. Saphir in this study.

ADDENDUM

After this study was completed, the following articles appeared:

Keith, N. M., Pruitt, R. D., and Baggenstoss, A. H.: Electrocardiographic Changes in Pericarditis Associated With Uremia, *AM. HEART J.* 31: 527, 1946. (The authors demonstrated how uremic pericarditis may undergo exacerbations and remissions and may even heal.)

Finch, C. A., Sawyer, C. G., and Flynn, J. M.: Clinical Syndrome of Potassium Intoxication, *Am. J. Med.* 1: 337, 1946. (The authors emphasized the clinical importance of the electrocardiographic changes in potassium intoxication in the differential diagnosis between conditions giving rise to paralytic states.)

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SEQUENCE OF VENTRICULAR STIMULATION AND CONTRACTION IN A CASE OF ANOMALOUS ATRIOVEN- TRICULAR EXCITATION

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ALTHOUGH hypotheses are numerous, many aspects of the phenomenon of anomalous atrioventricular excitation¹ (Wolff-Parkinson-White syndrome,² short P-R; bundle branch block syndrome,³ pre-excitation of the ventricles⁴) are not satisfactorily explained by existing data. The opportunity to study a man who displayed the abnormality intermittently provided answers for two unsettled questions: (1) Is the interval from the beginning of the P wave to the junction of the initial and final ventricular deflections (P-J interval) really or just fortuitously the same during normal and anomalous ventricular excitation? This is equivalent to asking whether conduction by an accessory tract is always accompanied by simultaneous conduction to the ventricles by the normal pathways. (2) What is the mechanical behavior of the ventricles when excitation is anomalous?

OBSERVATIONS ON VENTRICULAR EXCITATION

The patient was a healthy, 27-year-old white man of hypersthenic habitus, a truck driver by occupation, who had no cardiac complaints and whose cardiac examination was negative except for the accidentally discovered electrocardiographic abnormality to be noted.

Initial studies were made on Nov. 5, 1938. The standard leads (I, II, III), the extremity potentials (V_R , V_L , V_F), and the precordial potentials (V_1 , V_2 , V_3 , V_4 , V_5 , and V_6) were recorded simultaneously with Lead I with the subject recumbent. Two string galvanometers were used, one with a single stage vacuum tube amplifier in circuit. The rate of the auricles and of the ventricles did not fall below 52 per minute, and in this record no abnormal QRS deflections occurred. The standard leads were similar to the normal complexes shown in Fig. 2, a high T wave in Lead I being the only unusual feature. The electrical position of the heart determined from the extremity potentials was semivertical.⁵ The precordial potentials were within normal limits.⁶ On the same day the standard and special leads were repeated after the intravenous injection of 1.2 mg. of

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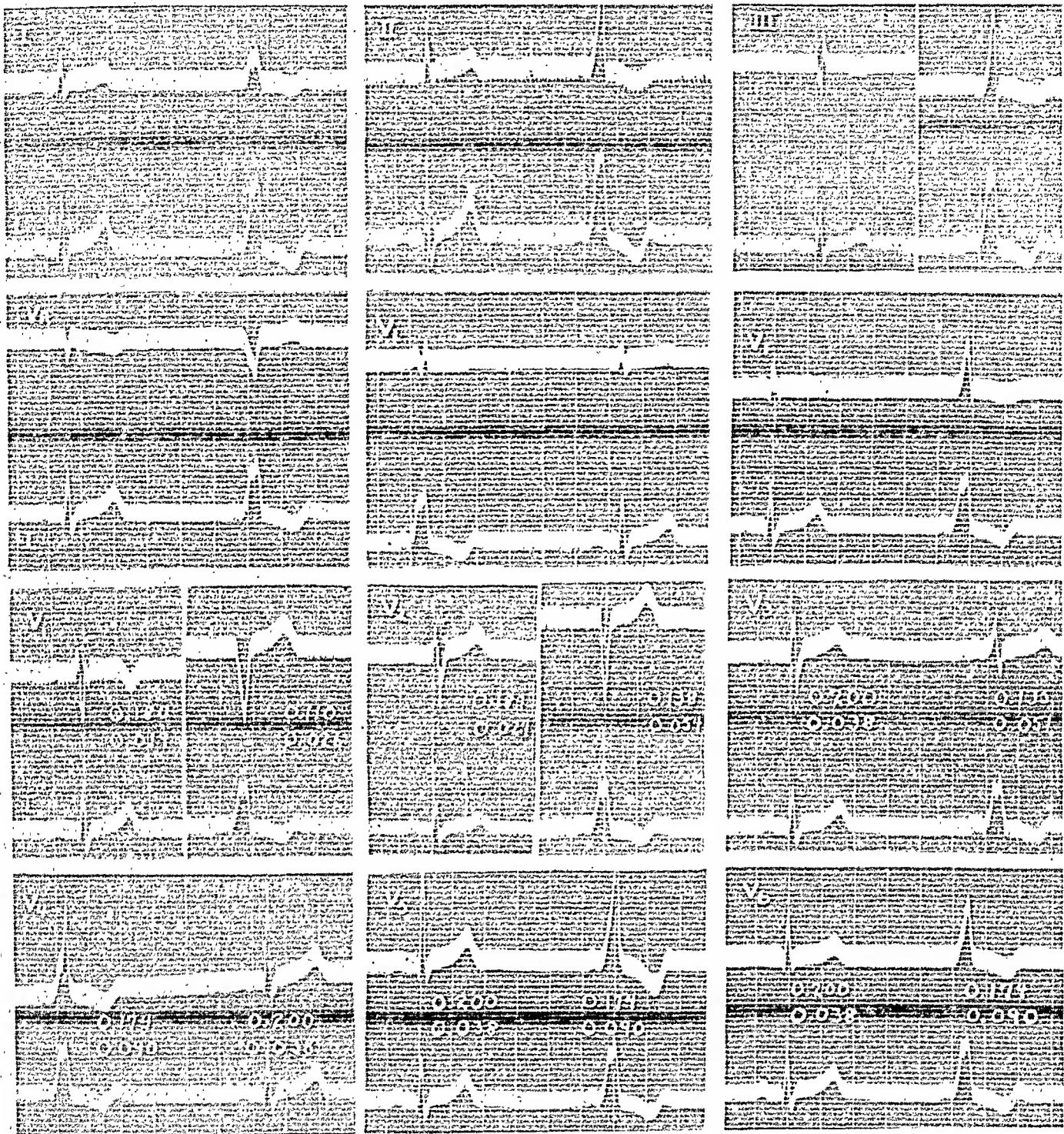


Fig. 1.—Standard and special electrocardiograms recorded on Jan. 21, 1939, with subject recumbent. A normal and abnormal QRS complex has been mounted for each lead. The upper records are: I, standard Lead I; II, standard Lead II; III, standard Lead III; VR, VL, VF are the potentials of the right arm, the left arm, and the left leg, respectively, made with Wilson's method; V1, V2, V3, V4, V5, and V6 are the potentials of the standard precordial points similarly made. The standard leads and extremity leads were made with the string at normal sensitivity (1 mv. = 1 cm.); the precordial leads were made at half normal sensitivity (1 mv. = 0.5 cm.). A vacuum tube was used in the circuit of the string when recording the curves.

The lower string shadow is standard Lead I recorded in the usual way with the string at approximately normal sensitivity but varying somewhat.

Under each precordial lead, both for the normal and abnormal QRS, there are two figures. The upper is the time in seconds from the beginning of P in Lead I to the beginning of the intrinsicoid deflection (peak of R) in the chest lead. The lower figure gives the time between the beginning of QRS in Lead I and the beginning of the intrinsicoid deflection in the chest lead.

atropine sulfate. Except for an increase in heart rate to 95 beats per minute, there were no significant changes.

A similar series of electrocardiograms (Fig. 1) was repeated on Jan. 21, 1939, after the subject had been at rest for a considerable period. When the ventricular rate was in the neighborhood of 50 beats per minute, occasional abnormal ventricular complexes appeared, and at times there were long runs of them alternating with normal ventricular deflections. Rate was not the only determining factor, however, because the QRS was sometimes normal in form even when the rate was below 50 per minute. Wherever possible an adjacent normal and abnormal QRS in the standard and special leads were mounted in Fig. 1 (upper string shadow), each having been recorded simultaneously with standard Lead I (lower string shadow).

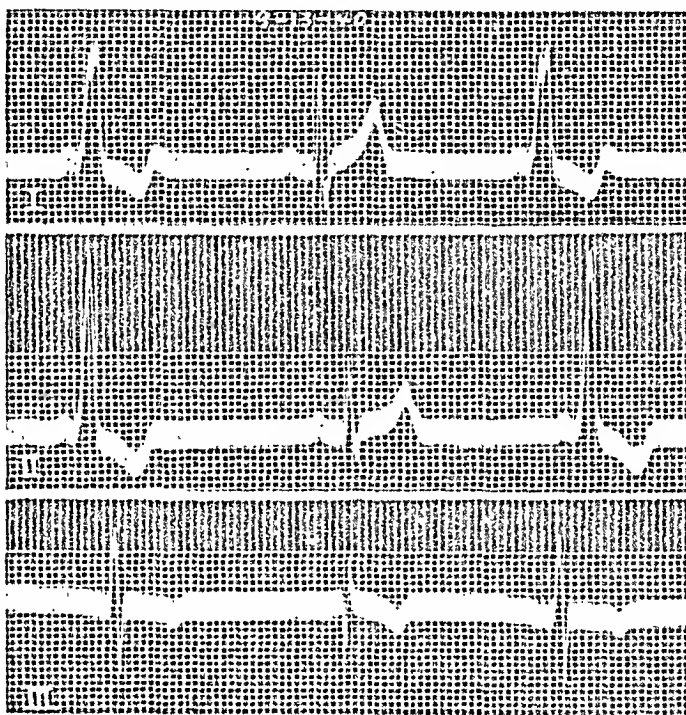


Fig. 2.—Standard leads recorded on Sept. 13, 1940, at a time when normal and abnormal atrio-ventricular excitation were alternating. In this record the time marker was approximately 4 per cent too fast.

The anomalous complexes, compared with the normal ones in Leads I and II, were characterized by a tall R wave with slurred ascending limb ("anomalous component"),¹ an absence of Q and S waves, and an inversion of T wave which was partial in Lead I. In Lead III, R was larger, the S deeper, and R' absent; the T wave in this particular record was deeper. There was no difference in the P waves preceding the two types of QRS.³

Various intervals (Table I) in the standard leads of this curve were determined by means of a comparator. Leads I and II were measured, but only the results of the former are shown because Lead I lent itself best to precise deter-

TABLE I. INTERVALS IN SECONDS IN STANDARD LEAD I OF RECORDS MADE ON JAN. 21, 1939, AND SEPT. 13, 1940

DATE	P-Q (P-R)		P-R PEAK		P-J		QRS		P-END T		Q-T		K	
	N	A	N	A	N	A	N	A	N	A	N	A	N	A
Jan. 21, 1939	0.154	0.079	0.200	0.174	0.251	0.233	0.097	0.156	0.556	0.530	0.402	0.451	0.367	0.411
Sept. 13, 1940	0.181	0.101	0.226	0.202	0.291	0.272	0.110	0.171	0.623	0.603	0.442	0.502	0.394	0.433

N, normal QRS; A, abnormal QRS resulting from anomalous atrioventricular excitation. Designation of intervals have the usual meaning. P-J was measured from the beginning of the P wave to the junction of QRS with the RS-T segment. K is the systolic Index ($Q-T/\sqrt{R-R}$).

mination of the beginning of the P and the end of QRS in both normal and abnormal records. The table reveals that during anomalous atrioventricular excitation the QRS interval was 0.059 second longer, the P-R (P-Q) interval was 0.075 second shorter, the P-R peak interval, 0.026 second shorter, and the P-J interval, 0.018 second shorter. The Q-T interval (duration of electrical systole) was much longer in the abnormal QRS and simulated in this regard the findings in bundle branch block.

The potentials of the extremities (V_R , V_L , V_F) revealed that the semivertical, electrical position of the ventricles was unchanged by anomalous excitation. Also, with the latter, the small positive component of Lead V_R and the initial negative component (Q) of Lead V_F disappeared.

In the chest leads the R wave of the anomalous complexes was vestigial in Leads V_1 and V_2 , and in this respect the records resembled those which have been designated as "Type B".¹ For each chest lead the time of the intrinsicoid (RS) deflection⁷ with respect to the beginning of the P wave in Lead I is indicated by the upper number, and with respect to the beginning of the QRS in Lead I, by the lower number. These are tabulated in Table II.

TABLE II. TIME IN SECONDS OF THE INTRINSICOID (RS) DEFLECTION IN THE PRECORDIAL LEADS WITH REFERENCE TO THE BEGINNING OF P AND THE BEGINNING OF QRS IN LEAD I WITH NORMAL AND ANOMALOUS ATRIOVENTRICULAR EXCITATION

LEAD	AFTER BEGINNING OF P_1				AFTER BEGINNING OF QRS_1			
	(1) NORMAL QRS	(2) ABERRANT QRS	(3) DIFFER- ENCE	(4) MEAN OF DIFFER- ENCES	(5) NORMAL QRS	(6) ABERRANT QRS	(7) DIFFER- ENCE	(8) MEAN OF DIFFER- ENCES
V_1	0.180	0.110	-0.070	-0.061	0.019	0.026	0.007	0.019
V_2	0.189	0.138	-0.051		0.027	0.054	0.027	
V_3	0.200	0.135	-0.065		0.038	0.051	0.013	
V_4	0.200	0.174	-0.026	-0.026	0.038	0.090	0.052	0.052
V_5	0.200	0.174	-0.026		0.038	0.090	0.052	
V_6	0.200	0.174	-0.026		0.038	0.090	0.052	

- a. Difference of means, Columns (1) and (5) = 0.162 (mean P-R interval, normal QRS).
 b. Difference of means, Columns (2) and (6) = 0.084 (mean P-R interval, aberrant QRS).
 Difference between a and b = 0.078.

Reference to Table II (Columns 1 to 4) and Fig. 1 reveals that excitation reached all anterior surfaces* of the heart earlier with anomalous excitation. If Leads V_1 and V_2 are regarded as having been from the right ventricle, and Leads V_4 , V_5 , and V_6 as being from the left ventricle, then the action current with anomalous excitation reached the right side 0.061 second, and the left side 0.026 second earlier than with normal conduction. When the reference point used

*This statement assumes that the peak of the R wave (beginning of the intrinsicoid deflection) marks the time of arrival of excitation at that part of the epicardial surface closest to the exploring electrode. This is probably correct for the greater surface of the left ventricle in man but there is evidence that other variables may be involved in the creation of this deflection over the right ventricle.

was the beginning of QRS in Lead I, then excitation reached the anterior surfaces of the heart later. Referring again to Table II (Columns 5 to 8), with aberrant conduction the intrinsicoid deflection was later on the right side by 0.019 second, and on the left side by 0.052 second.

The "transitional zone"⁸ was moved farther to the left with anomalous excitation as usually happens when block of the left bundle branch develops.

These data may be summarized as follows: Although accession began in the ventricles about 0.078 second earlier with anomalous atrioventricular excitation, it did so in a place remote from the normal pathways, for it reached the surface of the right ventricle about 0.017 second later than expected (0.078 - 0.061), and it reached the surface of the left ventricle 0.052 second later than expected (0.078 - 0.026). By measurement from the beginning of ventricular excitation these figures became 0.019 second and 0.052 second, respectively.

On Sept. 13, 1940, the standard leads were repeated (Fig. 2). These differed from previous records in that the normal QRS interval measured 0.110 second compared to 0.097 second on Jan. 21, 1939. At least some of this difference could be accounted for by the difficulty encountered in delineating the end of the S wave, and the remainder by the fact that the telechron timer on the different instrument used was fast by approximately 4 per cent. Although the general contour of both records was the same, there were other differences in intervals as shown in Table II.

In both records the P-J interval was shorter during abnormal excitation by 0.018 and 0.019 second, respectively (Table I), although the R peak of the abnormal QRS was 0.026 second earlier in Leads I, V₄, V₅, and V₆ on the first date (Table I and II), and 0.024 second earlier in Lead I on the second date. This difference was attributable to the longer interval (0.008 second on measurement) from the peak of R to the end of QRS (or J) in the aberrant complexes. This would mean that anomalous atrioventricular depolarization continued in other parts of the ventricles for a longer time after it reached the epicardial surface of the left ventricle than was the case when conduction was through the normal junctional tissues.

OBSERVATIONS ON VENTRICULAR CONTRACTION

Also on Sept. 13, 1940, stethograms were recorded simultaneously with Lead II and with a sphygmogram of the right carotid artery* at a time when anomalous and normal atrioventricular excitation were occurring alternately (Fig. 3). A stethogram at the apex (upper curve) showed only slight differences in the first (S₁) and second (S₂) sounds with the two types of conduction. At the pulmonic area changes were more definite even though the record (lower curve) was somewhat distorted by low amplitude noise. The most interesting differences were the lower amplitude of the first sound and the split second sound with normal conduction. The latter was the reverse of what might be expected.⁹⁻¹¹

*Records were made with an All-Electric Hindle (Cambridge Instrument Co.). Latency of the sphygmograph was 0.008 second both for the application and discontinuance of a mechanical stimulus.

The right carotid sphygmogram, corresponding to the two types of electrocardiograms, did not differ with regard to amplitude, inclination of the anacrotic limb, or general contour. However, the time of ejection did vary.

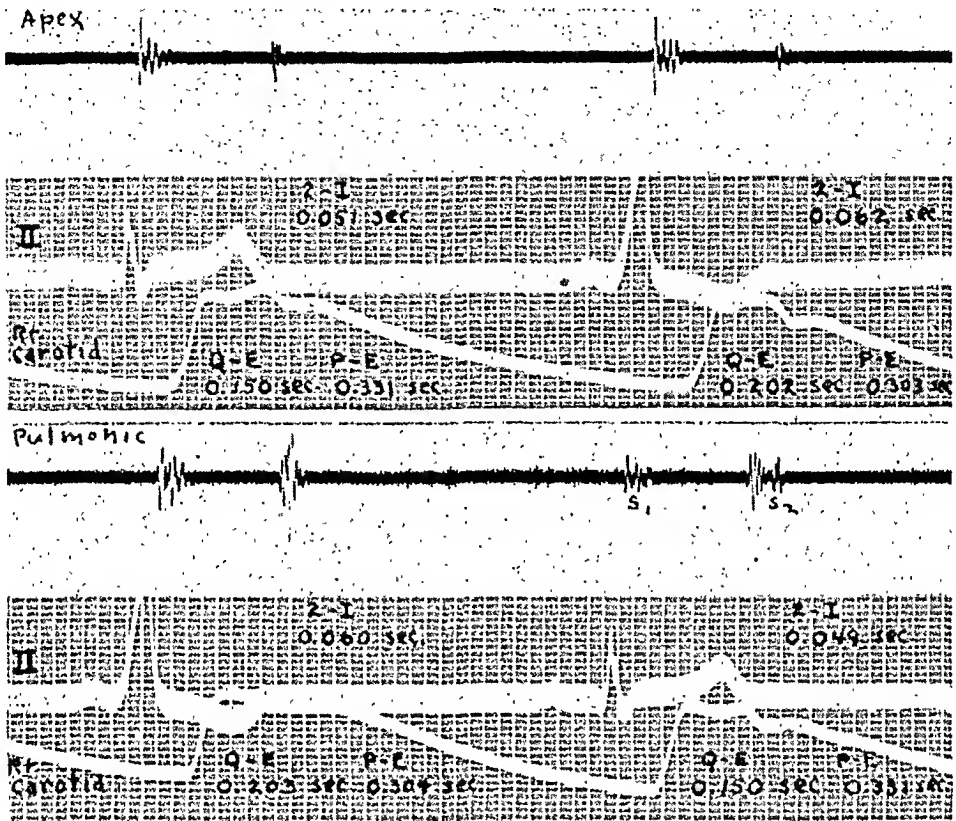


Fig. 3.—Simultaneously recorded stethogram (apex, upper curve; pulmonic area, lower curve), electrocardiogram (Lead II), and right carotid sphygmogram. "Q-E" was measured from the beginning of QRS to the beginning of the rise of the carotid curve; "P-E" was measured from the beginning of the P wave to the beginning of the carotid rise; and "2-I" was measured from the beginning of the second sound to the deepest part of the dicrotic notch (inscursa).

The low amplitude, high frequency vibrations on the lower stethogram were caused by outside noise.

In Fig. 3 the "P-E" interval was measured from the beginning of the P wave in Lead II to the beginning of the rise of the carotid pulse curve; the "Q-E" interval was measured from the beginning of QRS also to the beginning of ejection; and the "2-I" interval was measured from the beginning of the second sound to the deepest part of the dicrotic notch (inscursa) of the sphygmogram.⁹⁻¹² Comparative figures are the most significant especially in view of the electrocardiographic data already given. Relative to the time of discharge of the sinoauricular node (P-E interval), ejection was earlier with aberrant conduction by 0.027 to 0.028 second, but relative to excitation of the ventricular muscle it was 0.052 to 0.053 second later. These figures are almost identical with figures expressing the difference in time of arrival of excitation at the epicardial surface of the left ventricle with the two types of excitation (Table II). This would indicate that anomalous atrioventricular excitation affected both electrical and

mechanical events, at least in the left ventricle, in the same direction and to the same extent. Latency of the sphygmograph and probably of the velocity of the pulse wave from the heart to the carotid artery were constant for both types of conduction and hence play no part in the calculations as made.

Absolute values of the Q-E interval and the 2-I interval are to be compared with similar values obtained in normal subjects and in a few patients with left or right bundle branch block (Table III). Identical equipment was used in making these records. In the aberrant complex (Fig. 3) the Q-E interval of approximately 0.203 second and the 2-I interval of approximately 0.062 second simulate the findings with block of the left bundle branch (Table III).

TABLE III. MINIMUM, MAXIMUM, AND MEAN VALUES IN SECONDS OF THE Q-E INTERVAL (BEGINNING OF QRS TO BEGINNING OF CAROTID EJECTION) AND THE 2-I INTERVAL (BEGINNING OF SECOND SOUND TO DEEPEST POINT OF DICROTIC NOTCH), USING THE RIGHT CAROTID PULSE AND STANDARD LEAD II IN NORMAL SUBJECTS AND IN PATIENTS WITH LEFT AND RIGHT BUNDLE BRANCH BLOCK*

		NORMAL (8 SUBJECTS) QRS INT.: 0.064 TO 0.080	LEFT BUNDLE BRANCH BLOCK (3 PATIENTS) QRS INT.: 0.125 TO 0.168	RIGHT BUNDLE BRANCH BLOCK (5 PATIENTS) QRS INT.: 0.126 TO 0.145
Q-E	Minimum	0.131	0.195	0.120
	Maximum	0.148	0.233	0.180
	Mean	0.1392	0.2127	0.1508
2-I	Minimum	0.047	0.063	0.022
	Maximum	0.060	0.084	0.060
	Mean	0.0521	0.0770	0.0400

*The same apparatus was used as in making the records shown in Fig. 3.

By way of summary, the stethographic and sphygmographic data indicate that with anomalous atrioventricular excitation in this subject there was asynchronous contraction of the ventricles. Although in point of absolute time, measured from the initial discharge of the sinoauricular node, the left ventricle ejected blood earlier than normal, with respect to beginning depolarization in the ventricle it ejected blood later than normal and in this regard simulated conditions found when there is block of the left bundle branch.

DISCUSSION

The data presented favor the conclusion that in this subject anomalous atrioventricular excitation was not accompanied by conduction through the bundle of His as in previously reported cases.¹ Specifically two groups of facts lead to this conclusion: (1) All electrical events were earlier in both ventricles with pre-excitation than with normal conduction. These events include the beginning and end of QRS and the peak of R both in the standard and the precordial leads. (2) When the P-R interval was short the left ventricle

was depolarized (and repolarized) completely in a right to left direction as with block of the left bundle branch. The evidence for this was the prolongation of electrical systole (Q-T interval), the considerable delay from the time excitation entered the ventricles until it reached the epicardial surface of the left ventricle, and the stethographic and sphygmographic evidence of delayed ejection of the left ventricle. That the anomalous complexes differed in contour from the usual pattern seen with left bundle branch block does not seem to be a valid objection. In fact, a difference would be expected by virtue of the different manner of excitation of the contralateral ventricle in this syndrome compared to bundle branch block.

The mechanism by which conduction from auricles to ventricles was accomplished, exclusive of the usual pathways, seemed to depend upon the relative prematurity of conduction by the anomalous pathway, if such exists. Presumably, excitation entered the right ventricle so early that it had already spread in an aberrant fashion to the left ventricle, and that chamber was refractory at a time when an impulse reached it through the common bundle and left bundle branch.

Whether this always occurs in the type of electrocardiogram under discussion when the P-R interval is shortened beyond a certain "critical value" is not known. Existing data suggest that it should occur when the P-R interval with the anomalous complex is shortened by approximately 0.06 second or more.

This figure was arrived at in two ways, both concerned with determining how long it takes excitation to spread from one side of the human heart to the other as when a bundle branch is blocked. First, an approximation was made by comparing the QRS interval in the electrocardiograms of ten patients before and after the development of complete (QRS interval of 0.12 second or more) bundle branch block, either left or right. Admittedly, many variables come into

TABLE IV. TIME (SECONDS) OF AURICULOVENTRICULAR AND INTRAVENTRICULAR CONDUCTION IN REPORTED CASES OF INTERMITTENT ANOMALOUS ATRIOVENTRICULAR EXCITATION

AUTHORS	CASE	NORMAL CONDUCTION			ABNORMAL CONDUCTION			DIFFERENCE IN P-R INTERVALS
		P-R	QRS	SUM	P-R	QRS	SUM	
Wolf, Parkinson, White 1930 ²	1	—	—	—	—	—	—	0.06
	2	—	—	—	—	—	—	0.05
	3	—	—	—	—	—	—	0.10
	4	—	—	—	—	—	—	0.06
	8	—	—	—	—	—	—	0.06
Moia and Inchauspe, 1938 ¹⁴	—	0.16	0.06	0.22	0.09	0.12	0.21	0.07
Hunter, Papp, Parkinson, 1940 ³	3	0.14	0.08	0.22	0.12	0.11	0.23	0.02
Wolferth and Wood, 1941 ¹⁸	A. B.	0.17	0.08	0.25	0.13	0.11	0.24	0.04
Missal, Wood, Leo, 1946 ¹⁹	—	0.16	0.08	0.24	0.11	0.12	0.23	0.05
Rosenbaum, Hecht, Wilson, Johnston, 1945 ¹	5	0.160	0.078	0.238	0.122	0.122	0.244	0.038
Kossmann and Goldberg, 1946	—	0.154	0.097	0.251	0.079	0.156	0.235	0.075
	—	0.181	0.110	0.291	0.101	0.171	0.272	0.080

such a calculation, particularly relative hypertrophy of the interventricular septum and the chambers. Nevertheless, in the ten cases investigated the minimum lengthening of QRS by block of a bundle branch was 0.04 second, the maximum was 0.09 second, and the mean was 0.060 second. Second, the records published by Barker, Macleod, Alexander, and Wilson¹³ obtained by stimulating the exposed human heart were measured grossly with a hand lens. The supraventricular QRS was 0.08 second in length; the QRS interval of premature systoles induced in either ventricle was 0.13 to 0.14 second.

To test the concept further an attempt was made to learn what the usual shortening of P-R interval was in published cases of intermittent anomalous atrioventricular excitation. Unfortunately, most authors have not provided these data. Table IV contains published measurements found and also gross measurements made by us on electrocardiograms reproduced in several published articles, using the lead in which the normal P-R interval was longest. It simply shows, with three exceptions including the present case, that excitation of the ventricles in the syndrome under consideration is usually premature by less than 0.06 second. In one of the three exceptions¹⁴ asynchronous contraction of the ventricles was demonstrated. In the case reported here anomalous ventricular excitation was premature by an average of 0.078 second in two records made with an intervening interval of twenty months.

CONCLUSIONS

The findings presented favor the concept of an accessory pathway¹⁵⁻¹⁶ in anomalous atrioventricular excitation, and also help to explain some controversial matters. The variable reports^{14,17} on asynchronous contraction of the ventricles can be reconciled. Asynchronism will depend on the degree of prematurity of ventricular excitation. Further, the nature of the asynchronism will depend on whether the accessory pathway connects the auricles with the right ventricle or with the left ventricle.

Previous explanations¹⁷ for the occurrence of transitional complexes, such as published by Hunter, Papp, and Parkinson (Case 3), on the basis of a variable rate of conduction in the junctional tissues and the relative amounts of cardiac muscle stimulated through each pathway are favored by the findings in the present case. Possibly the failure to get much change in QRS with induction of A-V nodal rhythm in certain cases may also be based on very early excitation of the ventricles by the anomalous pathway whenever it functions. Under such circumstances shortening of the normal A-V conduction time would have only a partial effect. The findings also explain why in some cases with anomalous conduction and auricular premature systoles, the QRS complexes of the latter vary a little from those of the usual supraventricular beats.¹⁸

SUMMARY

1. In a case of intermittent anomalous atrioventricular excitation it was found that the interval from the beginning of the P to the end of the QRS was shorter with the anomalous than with the normal beats.
2. These and other data are interpreted to mean that depolarization of the ventricles was mediated entirely through an accessory pathway in the right

ventricle, and that there was no conduction through the normal A-V conduction system when the QRS complexes were anomalous.

3. Considerable delay in ejection of the left ventricle compared to the right occurred when the P-R interval was short.

4. It is suggested that in different individuals with the syndrome, and sometimes in the same individual, variations in the relative amounts of ventricular muscle excited by impulses reaching it through the normal pathway on the one hand and through an accessory bundle or bundles on the other, readily explains many observations which have heretofore been regarded as conflicting.

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THE VOLUME ELASTICITY OF THE AORTA IN THE INTACT DOG

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THE large elastic arteries act not only as conduits for the passage of blood, but serve also during systole as a storage point for part of the blood ejected by the heart. Through this mechanism these vessels accumulate energy during systole which they release during diastole. They form, therefore, a compression chamber or "Windkessel" which helps assure a constant flow of blood into the peripheral blood vessels. A large part of the heart's energy is used in filling this compression chamber.¹ The enlargement of the compression chamber is most rapid early in systole when the pressure within it is low,² but the compression chamber reaches its maximum size toward the end of systole.³ Most of the decrease in its size occurs early in diastole.⁴ The fluctuations in size of the compression chamber are determined by its distensibility which declines as the internal pressure rises. The elasticity of the various components of the compression chamber is unequal. Thus, the elasticity of the aorta diminishes toward the periphery.⁵ Age, also, causes a decline in its elasticity.⁶ The size of the compression chamber increases with the size of the animal in different species.⁷

It is thus apparent that the characteristics of the compression chamber play as important a role in cardiovascular dynamics as do those of the heart and peripheral resistance. Our information on the elastic properties of the large arteries has depended, to a large extent, upon studies of the isolated aorta and large vessels^{8,9} and upon indirect evidence involving measurements of pulse wave velocities and pressure pulses.¹⁰ There appear to be no direct observations of the distensibility or elasticity of the compression chamber or any of its component parts in the living animal, aside from the studies of Wiggers and Wegria,¹¹ who used an aortograph to determine the changes in diameter of one portion of the aorta simultaneously with the pressure changes in the root of the aorta. This impelled us to seek more information on this important physiologic subject. The newer techniques which have been developed in the study of angiography suggested that data on the size of the aorta might be obtained in intact animals and that from this data information concerning the properties of the compression chamber might be derived. In the present report we wish to describe a technique

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developed for the purpose of measuring the distensibility curve of the aorta in the living dog with chest closed. The findings so obtained are compared with the distensibility of the aorta found immediately after the death of the animal.

METHODS

Seven dogs weighing from 15 to 25 kilograms and anesthetized with nembutal (25 mg. per kilogram) were utilized in these studies. The portion of the descending thoracic aorta to be used for measurement was marked off with two small (1 cm. by $\frac{1}{2}$ cm. by $\frac{1}{2}$ mm.) metal grids which were sewed onto the adventitia at the level of the fourth and tenth intercostal spaces. For this purpose the aorta was exposed by two small openings on the left side of the chest, the dog meanwhile being maintained under artificial respiration. After placement of the grids the chest was closed, the pneumothorax relieved, and the animal permitted to breathe spontaneously. The animal was then heparinized by the intravenous administration of 3 to 4 c.c. of heparin,* after which two radiopaque catheters, 3.8 mm. in diameter, were introduced under fluoroscopic control. One was passed via the left carotid artery into the upper part of the ascending aorta. The other was passed via the left femoral artery into the descending thoracic aorta until its tip lay equidistant between the two grids; this catheter was then connected to a Hamilton manometer¹² to record the pressure pulse in the aortic segment to be studied. The upper catheter was used to inject Diodrast[†] for the x-ray visualization of the aorta. The animal, lying on its left side, was placed beneath the x-ray tube. Diodrast (20 c.c. of 70 per cent solution) was injected rapidly; immediately upon completion of the injection an x-ray picture (lateral view) was taken.[‡] The time of the x-ray exposure was recorded on the blood pressure record by means of a signal magnet. This was repeated a number of times without moving the animal or the x-ray tube. The x-ray photographs were taken at 25-inch tube distance, using 100 milliamperes, 75 kilowatts, and 0.1 second exposure. The dogs were bled from time to time in order to obtain a wide range of arterial pressures for each animal during the course of the experiment. This procedure was repeated until the animal succumbed.

Immediately after death the aorta was removed and the intercostal arteries tied close to the aorta; care was exercised to prevent constriction of the aortic wall by this maneuver. The upper end of the aorta then was tied off at the upper end of the proximal grid, and the lower end, at the lower end of the distal grid, was tied over a cannula attached to a syringe and a manometer. All the air in the system and aorta was withdrawn and replaced with physiologic saline solution. Measured increments of saline were injected into this isolated aorta and the resulting pressures measured on the manometer. After the desired maximal pressure was reached, enough fluid was removed to cause a return to atmospheric pressure. The measurements were repeated three times in succession. This procedure gave the pressure-volume (P/V) curve of the isolated aorta directly.

*We are indebted to Roche Organon, Inc., Nutley, N. J., for liberal supplies of Liquemin.

†We are indebted to Winthrop Chemical Co., Inc., New York, N. Y., for liberal supplies of Diodrast.

‡We are indebted to Dr. R. Arens, of the X-ray Department, for making available the facilities of his department.

The volume of the identical portion of the descending aorta in the living animal was calculated from the area and length of the aorta between the outer edges of the two grids in the lateral roentgenograms. The area was measured by planimetry after the margins of the aortic shadow were outlined in ink on the film. The planimeter reading was obtained at least five times for each film and the average recorded. The length of the aortic segment was measured with a flexible rule laid on the film halfway between the margins of the aortic shadow and curved to follow the curvature of the shadow. The average radius was computed from these two measurements. It was considered more accurate to obtain the average radius by computation of the aortic segment's area divided by twice the length than by direct measurement in several locations.

The volume of the aorta then was calculated as follows:

$$V = \pi \cdot r^2 \cdot K^2 \cdot lK = \pi \cdot r^2 \cdot K^3 \cdot l$$

where r and l are radius and length of the segment and K is a factor introduced to correct for the distortion of the x-ray tube. K was determined by dividing the known actual diameter of the lower catheter by the diameter of its x-ray shadow in the film.

The errors involved in this method of computing the volume of the aorta were checked in two isolated aortas filled with known increasing amounts of diodrast. Roentgenograms were taken of the aorta and of a catheter placed next to it, and the volume of the isolated aortas was calculated in the same manner as in the *in vivo* experiments. The results obtained were compared with the amount of fluid actually injected. The data given in Table I indicate a good agreement. An error which the control calculation does not reveal is due to the possibility that at low pressures the aorta may not be perfectly cylindrical so that the conversion of area to volume might be inaccurate. Furthermore, the

TABLE I. CONTROL OF THE CALCULATION OF AORTIC VOLUME IN VIVO

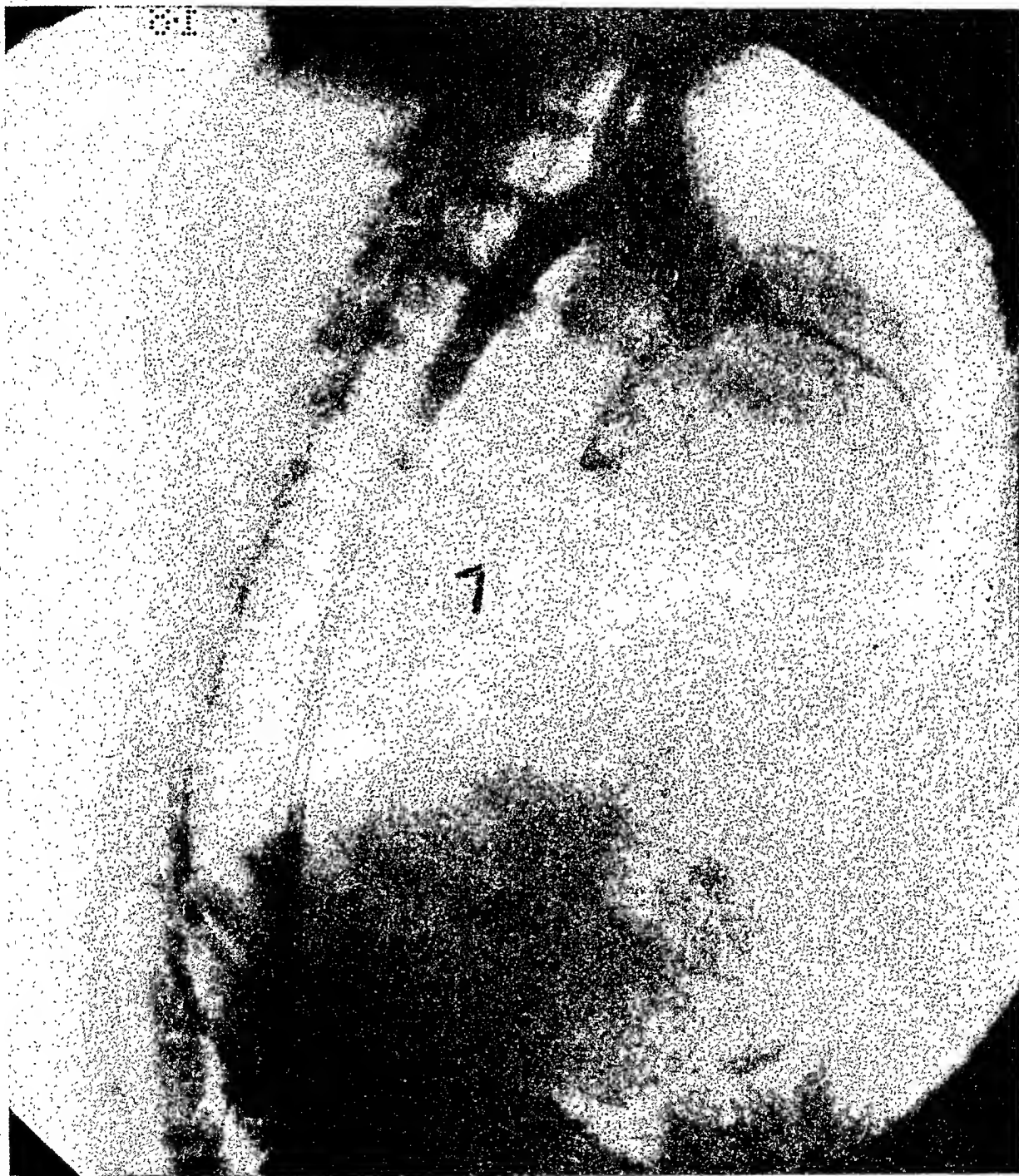
ACTUAL VOLUME INJECTED (C.C.)	VOLUME CALCULATED FROM X-RAY (C.C.)
<i>A. Isolated Aorta of Dog 10</i>	
4.0	4.4
5.0	5.3
6.0	6.2
7.0	7.1
8.0	8.4
<i>B. Isolated Aorta of Dog 22</i>	
2.6	2.7
3.6	3.5
4.6	4.6
5.6	5.5



A.

Fig. 1.—Roentgenograms of the diodrast-filled aorta in situ in the living dog (lateral view). *A*, Taken when the mean pressure in the thoracic descending aorta was 97 mm. Hg. *B*, Taken when the mean pressure in the thoracic descending aorta was 51 mm. Hg. *C*, Taken after the death of the animal, the aortic pressure being 0 mm. Hg. In each, the two catheters are seen in the aorta, the upper one passing down into the ascending aorta and showing diodrast escaping into the sinuses of Valsalva, the lower one passing up into the descending thoracic aorta with its opening halfway between the two grids (crosshatching) fastened to the aorta. The shadow of the heart and liver can be seen with diodrast filling the coronary and hepatic arteries. The filling of the aorta and these two systems of arteries are seen best in *C*, since absence of respiratory and cardiac motion and of blood circulation, respectively, makes for less fuzziness and less diodrast dilution. In *C*, the intercostal vessels are clearly visible. The visualization of the coronaries in life has been reported previously.¹³ The increase in the diameter of the aorta in *B* compared to *C* and in *A* compared to *B* is clearly seen. Comparisons of *A*, *B*, and *C* also show that increase in arterial pressure causes (1) a progressively greater distensibility of the aorta from the diaphragm to the semilunar valves; (2) an increase in the distance between the ascending and descending parts of the arch of the aorta; and (3) an elevation of the arch. The method of calculating the area of the thoracic aorta between the grids and converting it into volume is given in the text. Other details also are discussed in the text.

grids marking the limits of the aortic segment changed their angle as the size of the aorta altered (Fig. 1) and introduced an error in determining length. Another possible error inherent in our method lies in the determination of pressure. This was measured as the mean pressure by planimetry of the pressure-



B.

Fig. 1 (Cont'd).—For complete legend, see opposite page.

pulse curve, whereas the volume calculated is more likely to be the systolic volume. It has been shown that the pressure pulses in various parts of the aorta are not identical and to some extent this is true also of the segment of aorta under consideration. By taking the measurements in the middle of the

aortic segment, however, a close approximation of the average pressure in the segment should have been obtained. Finally, the catheter measured end pressure rather than the slightly lower lateral pressure actually impinging upon the aortic wall.

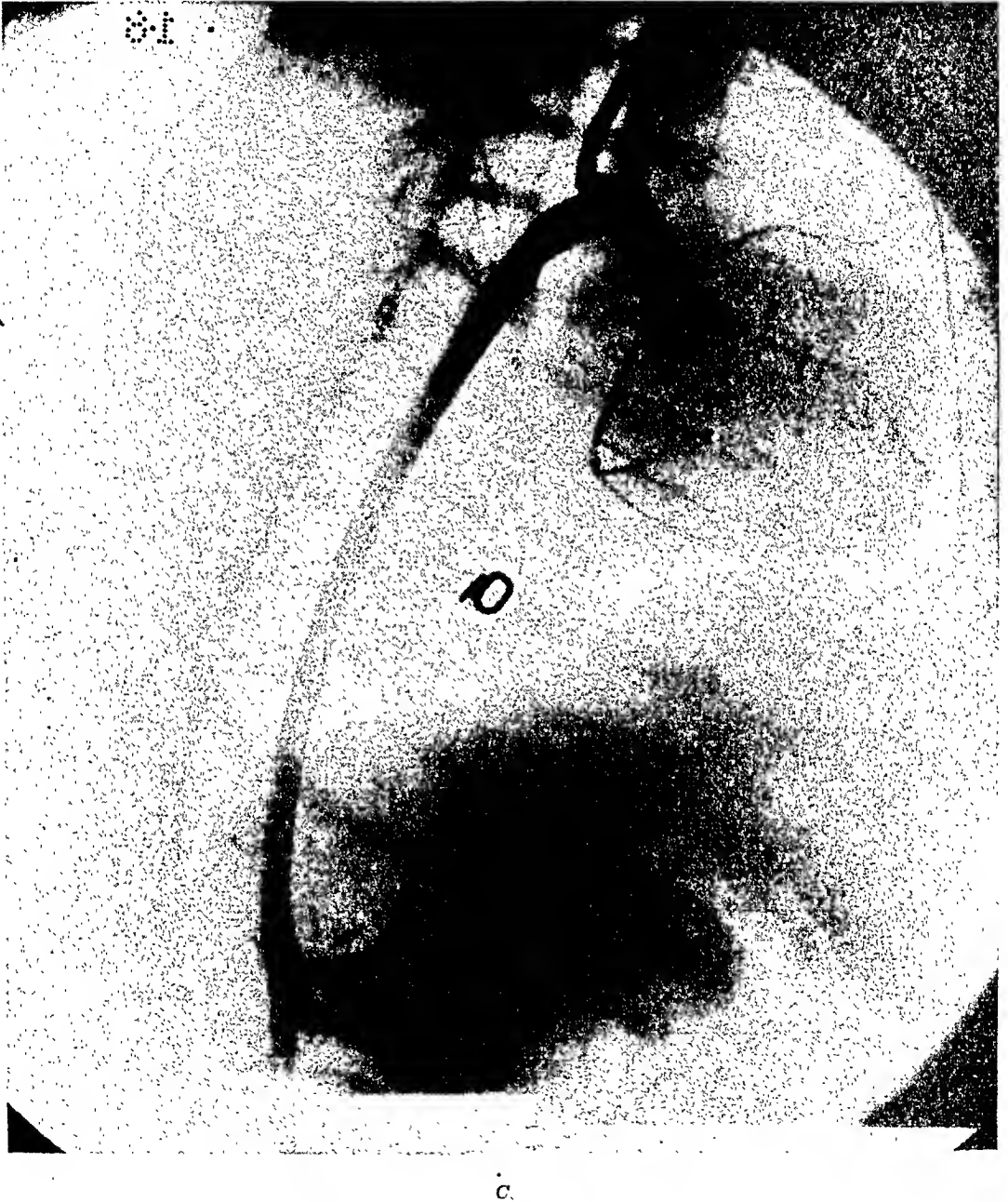


Fig. 1 (Cont'd).—For complete legend, see page 322.

The scatter of individual points from the pressure-volume curve obtained in vivo is attributable to several random errors. Among these are the following: (1) The movements of the grids mentioned cause the length measurement of different roentgenograms to vary from its true value; (2) the inaccuracy of outlining

the margins of the aortic shadow, together with the inaccuracy in the length measurements, causes the area outlined on the roentgenogram to vary from its true size; (3) the time of x-ray exposure, 0.1 second, is a variable part of the heart cycle, so that the mean pressure calculation based on the complete heart cycle will vary from the mean pressure actually existing during the x-ray exposure; (4) variations in the processing of the x-ray films may bring out varying degrees of diffusion which cause variations from their true dimensions in the shadow of the aorta and the catheter within it. From these considerations it is apparent that the measurements made in vivo are to be considered as approximations of the actual pressure-volume relationship. There is need for a more accurate approach, but the present method appeared to be sufficiently accurate to reveal trends.

In order to make the figures comparable, the volumes were converted to volumes for a standard length of aorta (10 cm.) by multiplying by ten divided by the actual length. The volume so obtained was plotted as percentage of the volume at 55 mm. Hg. These P/V curves were used as an index of the distensibility of the various aortas.

RESULTS

The P/V Curve of the Descending Thoracic Aorta in the Living Animal.—When the volumes of the aortas were corrected for standard length and plotted as percentages of the volume at 55 mm. Hg, the pressure-volume curves of the seven dogs fell into two groups of different slope, as shown in Fig. 2. In five

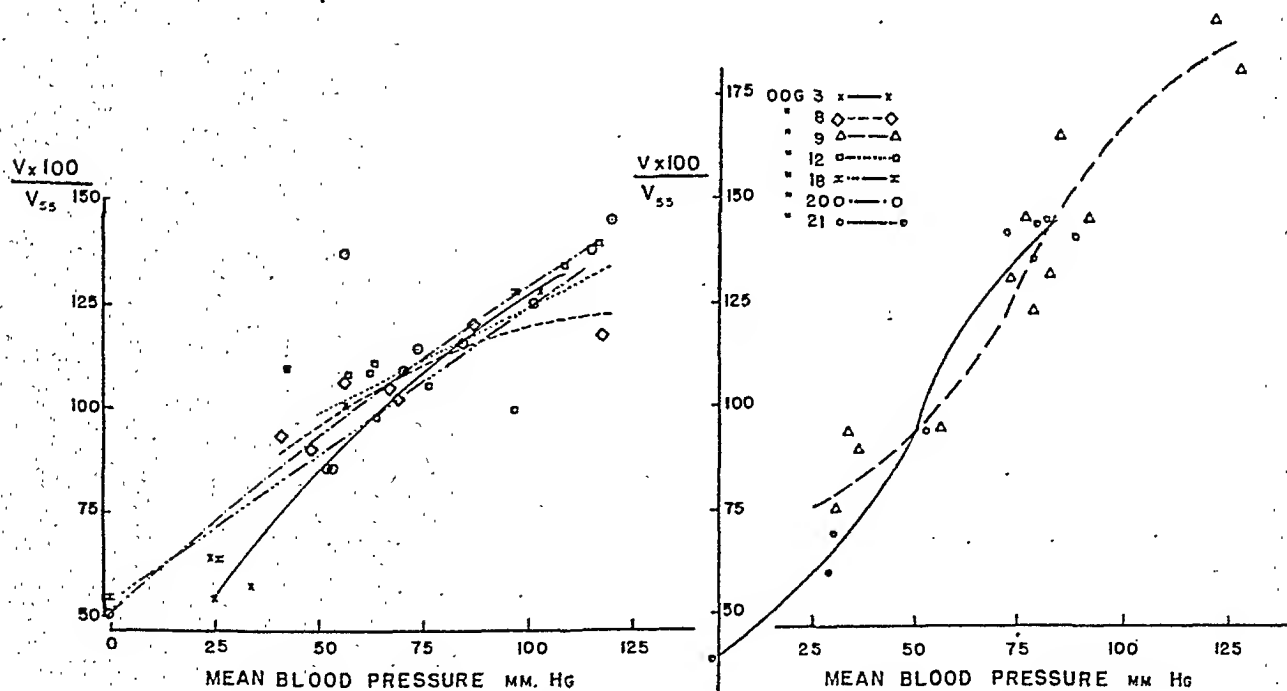


Fig. 2.—P/V curves as calculated for the descending thoracic aorta in seven living dogs. Discussed in text.

dogs the slopes coincided reasonably well, as shown on the left; in the other two dogs the slopes were much steeper, as shown on the right. Furthermore, the curves showed differences in contour. It is thus apparent that the inherent

distensibility of the aorta in vivo varies from animal to animal even after the differences due to different length and diameter are eliminated. These differences undoubtedly represent variations in the elasticity of the various components of the aortic wall. Age differences in the animals are probably not the sole influence.

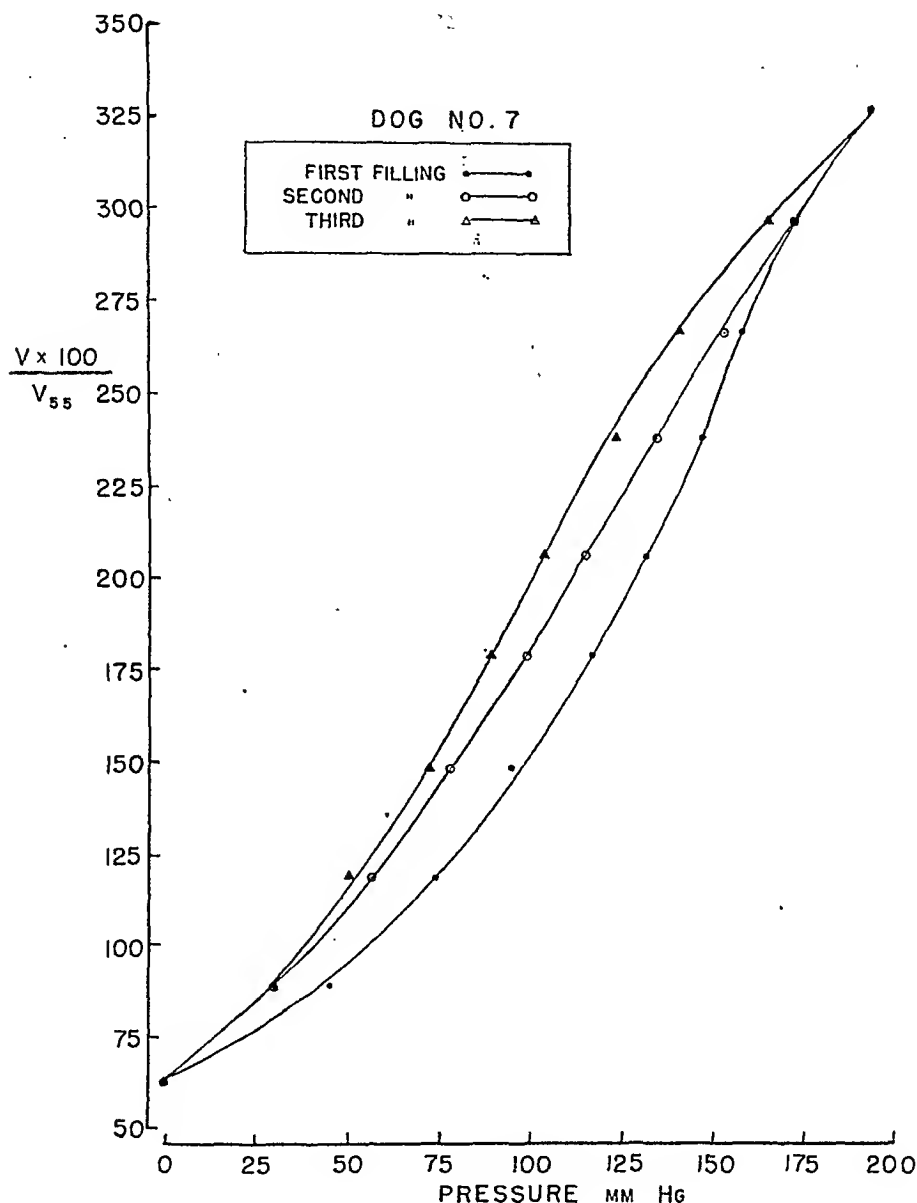


Fig. 3.—Dog 7. P/V curve of the isolated descending thoracic aorta in one dog showing the alteration in its contour in three successive fillings. Discussed in test.

The P/V Curve of the Isolated Aorta.—In confirmation of the finding of Kraska,⁸ we have found that repeated distention of the isolated aorta alters the shape of the P/V curve. A typical experiment is illustrated in Fig. 3. Volumes are again expressed as values at 10 cm. length and as percentage of the volume at 55 mm. Hg of the initial stretch. It will be seen that for the pressure

range between 0 and 200 mm. Hg, the P/V curve starts and ends at the same points for the three stretchings. In the second distention, however, intermediate points show a greater volume for a given pressure, and in the third a further increase of volume at these pressures is seen.

It was found that four of the five isolated aortas were remarkably alike (Fig. 4) when the P/V curves of the first distention were compared. The fifth aorta coincided with the others at lower pressures but showed less distensibility at higher pressures.

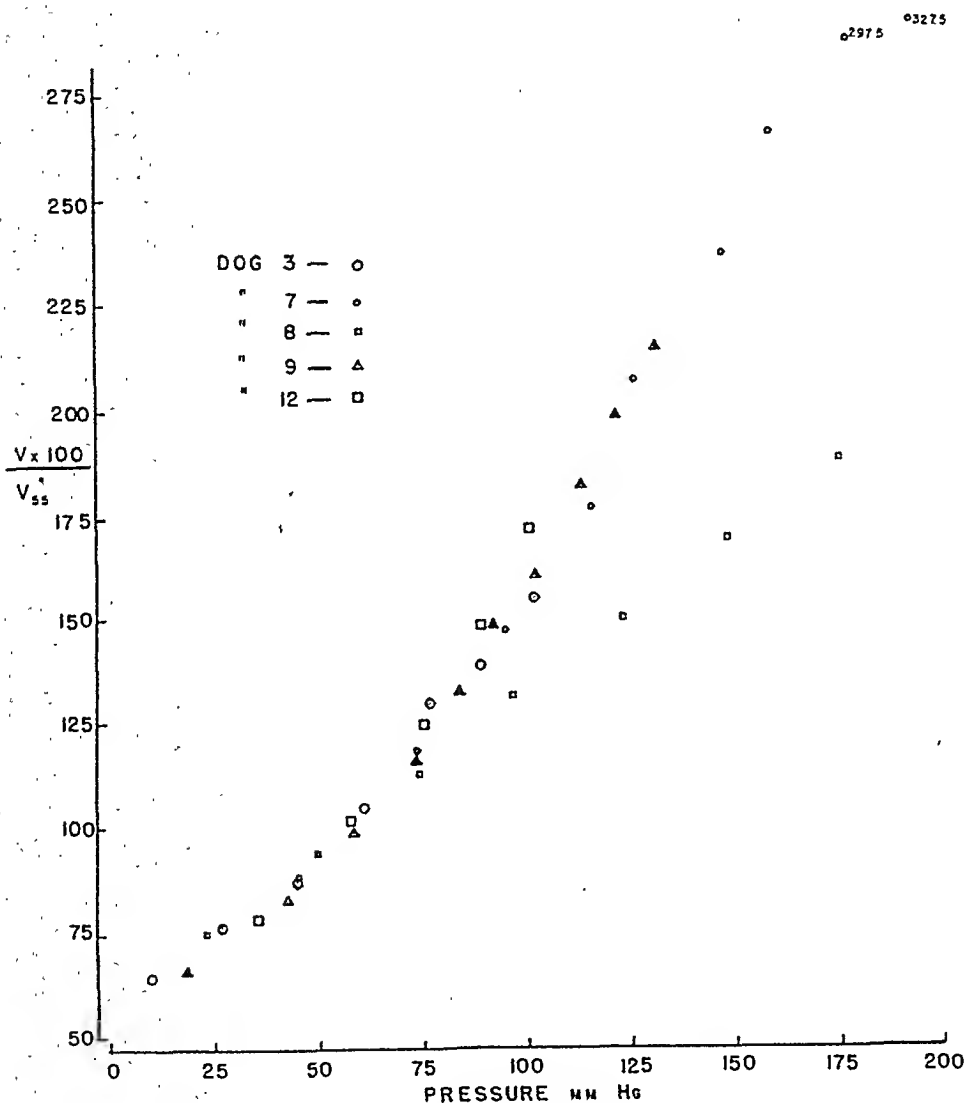


Fig. 4.—Initial filling P/V curves of the isolated descending thoracic aorta in five dogs. Discussed in text.

In four animals, the distensibility curve of the isolated aorta could be compared with that obtained in the living animal. This comparison is shown in Figs. 5, 6, 7, and 8. In the isolated aorta the values obtained for the first distention were used. It will be seen that the P/V curves obtained in living animals and in isolated aortas differ from each other in slope in all cases, some more than the others. In all, there is a tendency for the aorta in vivo to be less distensible at higher pressures than the isolated aorta. In Dog 9, this difference is slight, in Dog 12 it is marked, and in the other two dogs it is intermediate.

The comparison between the distensibility curves in living and isolated aortas suggest that the distensibility of the aorta *in vivo* cannot be accurately determined by measuring the distensibility of the isolated aorta but must be determined in the intact animal.

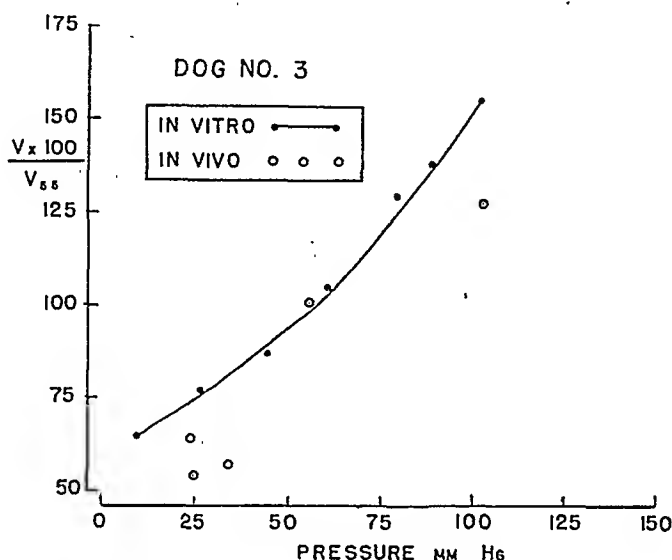


Fig. 5.—Dog 3. P/V curve obtained from *in vitro* initial distention of the descending thoracic aorta compared with the P/V values obtained *in vivo*. Discussed in text.

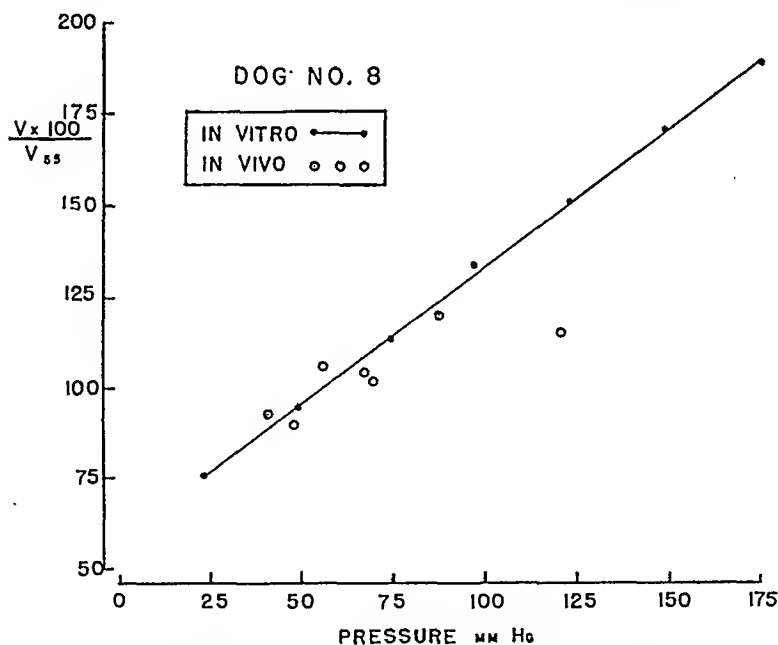


Fig. 6.—Dog 8. P/V curve obtained from *in vitro* initial distention of the descending thoracic aorta compared with the P/V values obtained *in vivo*. Discussed in text.

In explaining the difference between the *in vivo* and *in vitro* distensibility curve in the intact and isolated aorta, the difference in systolic uptake of the various parts of the aorta may play the significant role. Since the volume of the

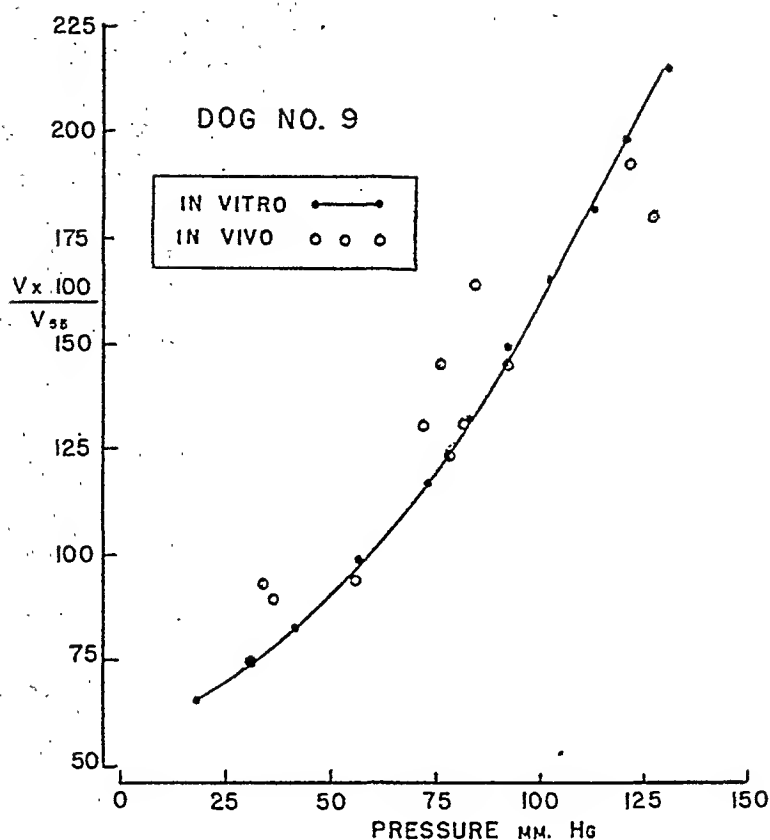


Fig. 7.—Dog. 9. P/V curve obtained from in vitro initial distention of the descending thoracic aorta compared with the P/V values obtained in vivo. Discussed in text.

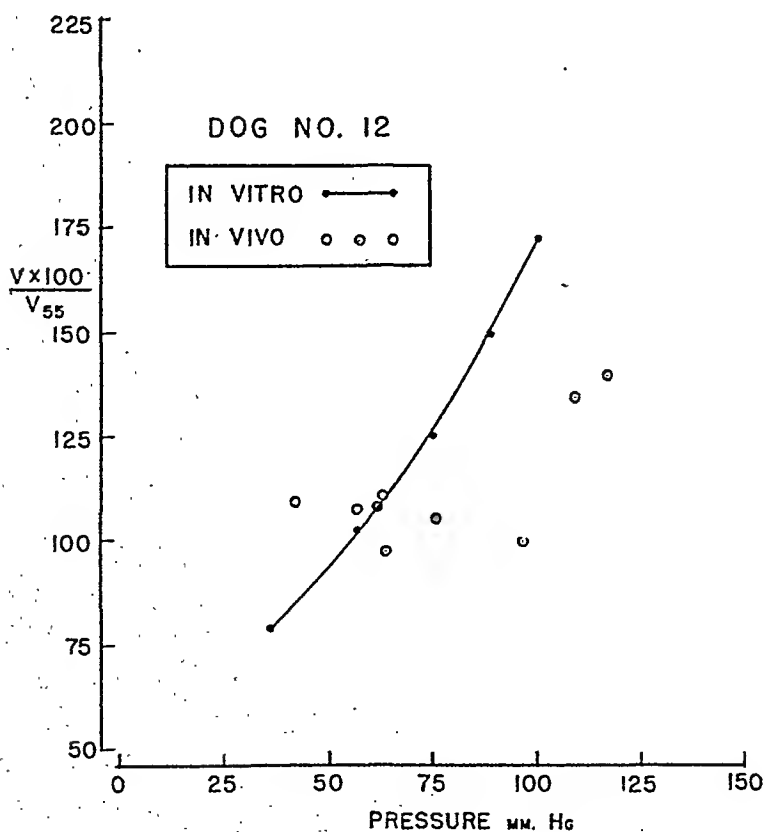


Fig. 8.—Dog. 12. P/V curve obtained from in vitro initial distention of the descending thoracic aorta compared with the P/V curves obtained in vivo. Discussed in text.

aorta so obtained in vivo is probably the systolic volume, differences in the distensibility of the parts of the compression chamber will mutually influence the systolic uptake of each part. Examination of Fig. 1 will show that the ascending aorta and arch are more distensible than is the descending thoracic aorta. This is associated not only with a much greater increase in diameter of the upper part of the aorta at higher pressures, but also with a greater separation of the anterior and posterior segments of the arch and a more cephalad placement of the arch.

SUMMARY

1. A new method for determining the volume of the descending thoracic aorta in the intact dog is described. This method makes use of diodrast-angiography and makes possible the direct determination of the distensibility of the aorta in the living animal.

2. Data depicting the pressure-volume relationship of this segment of the aorta in the intact dog were assembled from seven dogs. Similar data were obtained for the same segment of the aorta immediately after death in five dogs. The volumes were converted to standard length and diameter in order to compare the data of one animal with those of another and also to compare the data obtained in the living animals with those obtained in the isolated aorta.

3. The errors of the method are discussed.

4. It was found that in the living animal considerable variation existed from dog to dog in the contour of the pressure-volume (P/V) curve. The pressure-volume curve fell into two general slopes, however; the aortas of five dogs fell along the less distensible curve and the aortas of two dogs fell along the more distensible curve.

5. Consistent deviations were found in the pressure-volume curves in the isolated aortas obtained in three successive fillings. While starting and ending at the same point (at pressures of 0 and 200 mm. Hg), in each successive filling the aorta was more distensible at intermediary pressures.

6. The pressure-volume relationship of the first distention in four of five isolated aortas was remarkably uniform. That of the fifth aorta coincided with the P/V curve of the other four at lower pressures but deviated from it at the higher pressures.

7. The discrepancy between the pressure-volume relationship found in the living animal as compared with the more consistent P/V curve in the isolated aortas indicates that the distensibility of the aorta in vivo cannot be depicted accurately by measurements on the isolated vessel. This was confirmed by actual comparison of the P/V relationship of the aorta in vivo and the isolated aorta in four animals.

8. The differences between the distensibility curves of the intact and isolated aorta are attributed to the differences in systolic uptake of the various parts of the compression chamber. Such variation in distensibility of the parts of the aorta was readily discernible in the roentgenograms (lateral view) taken of the entire thoracic aorta. At increasing pressures the upper part of the aorta and the arch increased in size to a greater extent than did the lower descending thoracic aorta with which this study concerned itself.

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THE DIAGNOSIS AND TREATMENT OF THROMBOANGIITIS OBLITERANS IN THE VASCULAR CENTERS OF ARMY GENERAL HOSPITALS

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THE clinical and other features of thromboangiitis obliterans, as encountered in the Armed Forces, did not differ from those observed in civilian practice except that the condition was seen generally in the early stages and very few old, long-standing cases were encountered. The data which form the basis of this report were assembled from the three vascular centers (Fig. 1).*

CLINICAL FEATURES

Incidence.—Thromboangiitis obliterans constituted a small but appreciable proportion of the cases admitted to the vascular centers. Of a group of 3,778 vascular cases, the diagnosis of thromboangiitis obliterans was made in 274 patients, or 7.2 per cent of the total.

Duration of Symptoms.—In fifty-three cases reported from Ashford General Hospital, the average duration of symptoms was 21.9 months, the shortest duration being one month and the longest thirteen years. Occasionally, the diagnosis of thromboangiitis obliterans was made in one of the vascular centers only after the patient had been under examination and treatment in many installations in which a variety of diagnoses had been made. In such instances highly specialized diagnostic procedures, which included determinations of skin temperature, oscillography, and even arteriography or biopsy of the affected vessel, were required before the correct diagnosis was made.

Sex.—Thromboangiitis obliterans almost exclusively affects men, although occasional cases have been reported in which evidence of its presence has been found in women. There have been no reports from any of the vascular centers of its occurrence in women.

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*Major Jacob H. Kahn supplied the data from the Vascular Section, Ashford General Hospital. The material from the Vascular Surgical Section, Mayo General Hospital, was assembled by Lieutenant Colonel Harris B. Shumaker and that from the Vascular Medical Section, Mayo General Hospital, by Major David I. Abramson. Major John V. Waller compiled the figures from the Vascular Medical Section, DeWitt General Hospital. To each of these officers I wish to express appreciation for their helpful cooperation.

Race.—Although originally thromboangiitis obliterans was believed to occur chiefly in the Jewish race, subsequent investigations have shown that its occurrence is far more widespread. It has been encountered in individuals of every nationality. In the present series, of 150 patients in whom the race was recorded, thirty-two (20 per cent) were Jews. Although the disease supposedly is rare in the Negro, seven cases were reported from the vascular centers in which the diagnosis was confirmed by biopsy or by the typical clinical picture which the Negro patient presented.

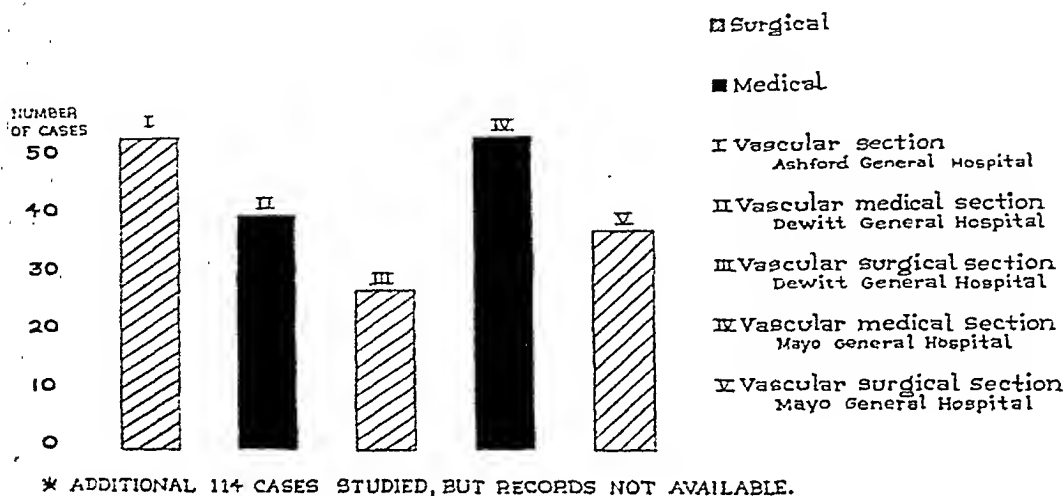


Fig. 1.—Sources of material on thromboangiitis obliterans.

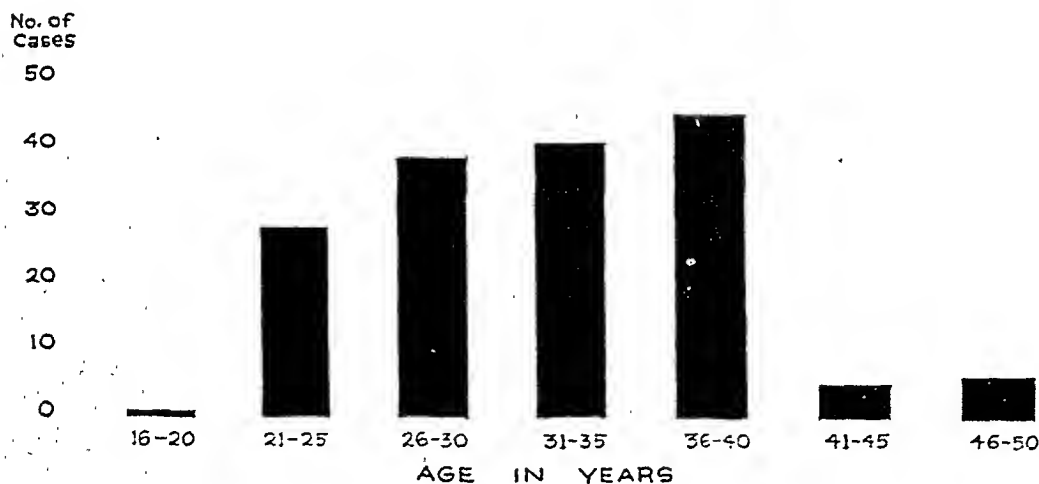


Fig. 2.—Age of patients with thromboangiitis obliterans.

Age.—In Fig. 2 is shown the age distribution in 152 of the patients with thromboangiitis obliterans. Ninety-two per cent of the cases fell within the age period 26 to 40 years. The relatively low reported incidence in patients under 25 years of age may be explained on the basis that the disease, although present, had not advanced sufficiently to produce symptoms.

Symptoms.—The symptoms presented by the patients at the time of admission are shown in Fig. 3. As can be seen, intermittent claudication, which Homans¹ has termed "the one characteristic early evidence of the disorder," was the complaint most frequently noted (67 per cent). This intermittent limp-

ing was most often associated with pain in the foot and leg. Sixty per cent of the patients complained of some form of pain in the extremities. Temperature difference, either subjective or objective, was observed in 45 per cent of the patients. Twenty per cent complained of some disturbance of sensation, chiefly numbness, especially after walking. Ulceration was present in 20 per cent, although gangrene was observed in only 4.4 per cent of the series. Vasomotor disturbances characteristic of Raynaud's phenomenon were observed in nine patients. Migratory phlebitis was found in slightly less than one-third of the patients. This incidence is approximately the same as that found in the statistical surveys reported in the literature.

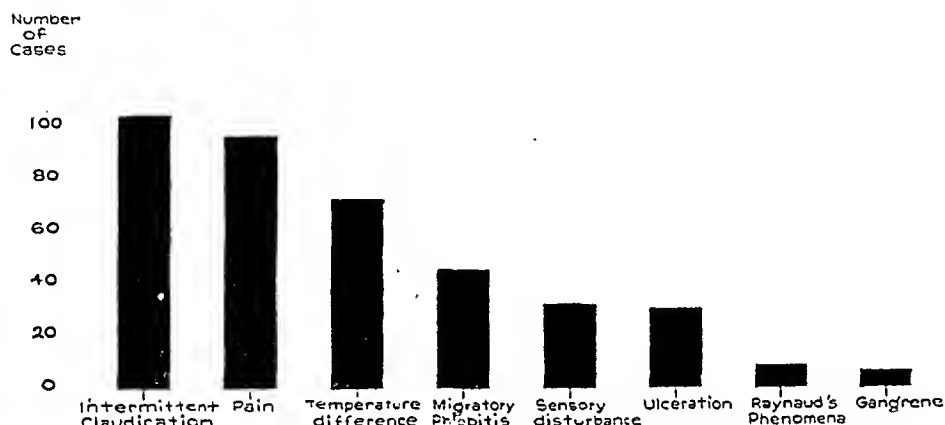


Fig. 3.—Symptoms on admission of patients with thromboangiitis obliterans.

Extent of Involvement.—Thromboangiitis obliterans is a systemic vascular disorder and although its clinical manifestations are generally most noticeable in one extremity, careful examination frequently reveals that blood vessels of other extremities are affected. Fig. 4 illustrates the number of extremities

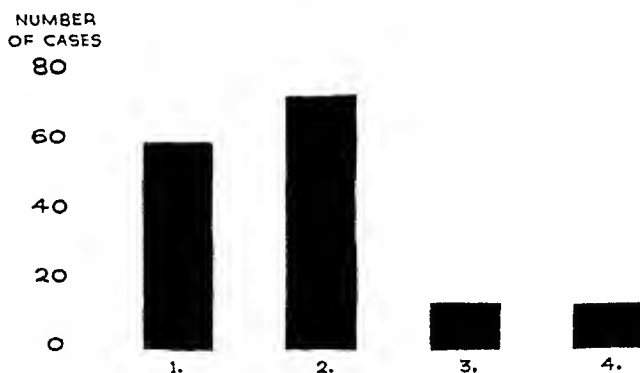


Fig. 4.—Number of extremities involved in patients with thromboangiitis obliterans.

involved in each of the patients. In 62.5 per cent two or more extremities were involved. There was evidence that all four limbs were involved in 13 patients (7.4 per cent). Despite the widespread character of the involvement, visceral

manifestations were rare. In three cases, attacks of precordial pain suggested disease of the coronary arteries. One patient who had suffered from thromboangiitis obliterans of the peripheral arteries for many years developed quadriplegia and other neurological manifestations which indicated that the cerebral vessels probably had been affected.

DIAGNOSTIC PROCEDURES

In addition to a complete history and physical examination in which particular attention was paid to clinical evidence of vascular disorders, certain special procedures were employed in order to establish the diagnosis of thromboangiitis obliterans. Constant temperature rooms were available in each of the vascular centers and also equipment for accurate measurement of skin temperatures and for the determination of oscillations from peripheral arteries. Fig. 5 gives the

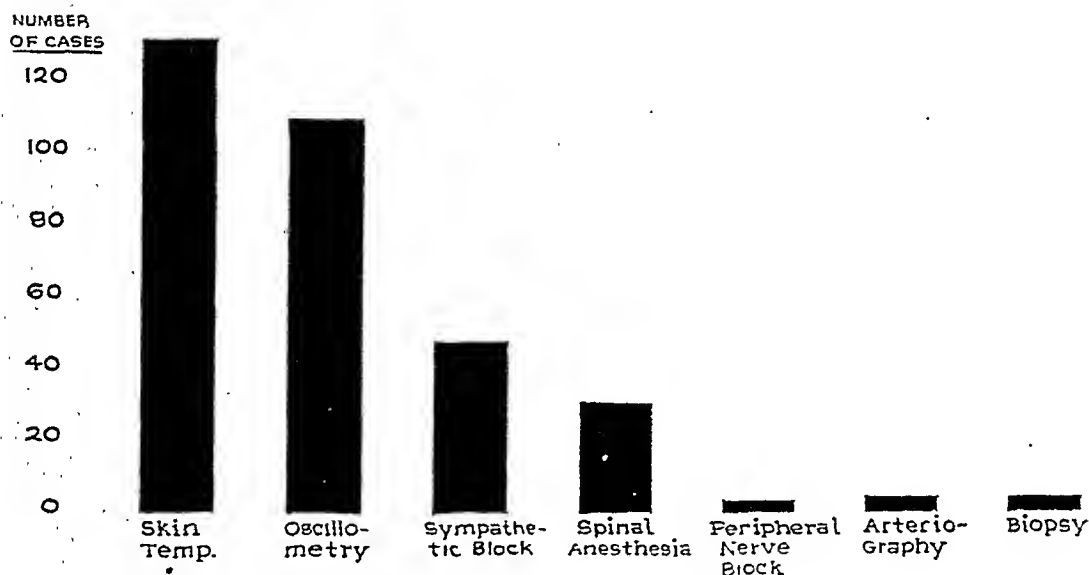


Fig. 5.—Number of diagnostic procedures employed in patients with thromboangiitis obliterans.

total number of special examinations conducted on the patients. Skin temperature studies and oscillometry after release of vasomotor tone by reflex vasodilatation, paravertebral injection of procaine, spinal anesthesia, or peripheral nerve block were especially useful in disclosing early involvement of the peripheral arteries and in the selection of patients for sympathectomy. Radiography after the intra-arterial injection of thorotrast was employed in four patients in whom early involvement of the vessels was suspected. The peripheral pulses were normally present in each of these patients. Arteriography demonstrated, however, that the circulation through these vessels was maintained by means of collateral vascular channels. Biopsy of the affected vessels substantiated the diagnosis in four other patients.

TREATMENT

It is generally agreed that no form of therapy for thromboangiitis obliterans is of use unless the patient completely stops smoking. In the analysis of therapy, therefore, primary consideration is given to this subject.

Smoking.—Ever since Erb² called attention to the close relationship between smoking and endarteritis, this aspect of the problem has been the subject of many clinical and scientific observations. Silbert,³ who has followed for over ten years 100 patients with thromboangiitis obliterans who gave up smoking completely, and who have shown absolutely no progression of the disease, has concluded that the disease "is caused by smoking in individuals constitutionally sensitive to tobacco." On the other hand, Homans¹ has stated: "There is no question that tobacco smoking has a decidedly bad influence upon the course of the disorder, but this does not imply that it necessarily is a cause." Although Silbert³ maintains that in his experience with 1,300 cases of thromboangiitis obliterans he has observed no case in patients who never had used tobacco, Horton⁴ has found the disease present in sixty-eight nonsmokers of a total of 948 cases. Four patients in the present series did not smoke.

Whatever may be the etiologic relationship between smoking and endarteritis, it is generally agreed that abstinence from smoking is mandatory. As Allen⁵ has remarked, "It is apparent that it is largely useless to treat patients who continue to use tobacco." Homans¹ has emphasized this fact: "Above all, if he will not abandon tobacco smoking, his disease will almost necessarily persist and indeed will probably be aggravated."

Specific information was obtained on this phase of the subject from the vascular centers on ninety-three patients with thromboangiitis obliterans. Of this number seventy-seven patients stopped smoking completely. Persistence of the disease was noted in two patients. By comparison, in the group of sixteen who admittedly continued to smoke, progress of the vascular obliteration was observed in eight patients.

In this discussion of the relationship between smoking and thromboangiitis obliterans, it may not be amiss to quote the opinions expressed by officers who have directed the medical investigations and care of large groups of patients with this condition in the vascular centers. Major Kahn, of Ashford General Hospital, wrote: "Our experience with the use of tobacco is as follows: While not the cause of thromboangiitis obliterans, smoking is a very aggravating factor. Unless the patient stops smoking completely, no form of treatment, including sympathectomy, is of benefit. Recurrent migratory phlebitis has disappeared with the cessation of the tobacco habit alone. Wounds and gangrenous areas have cleared rapidly, and rest pain has considerably improved when tobacco was stopped. Following sympathectomy, the patients who still smoked complained of pain which was quickly relieved when the habit was stopped. Gangrenous areas were slow in healing and demarcating when the use of tobacco was continued after sympathectomy. Gratifying results were noticed when smoking was stopped."

Major Abramson, of Mayo General Hospital, stated: "It was definitely felt that no medication would be of any value if the patient was not abstaining from smoking. When the diagnosis of thromboangiitis obliterans was made on a patient, the nature of the disease was thoroughly discussed with him and the dangers of continuing to smoke were graphically illustrated to him by showing him the extremities of patients in an advanced stage of the disease. Most of the patients, when informed of the relationship of smoking to the progress of the disease, stated that they would abstain completely. However, in a number of instances it was subsequently brought to our attention that they had not been too serious in their pledge."

As Silbert⁶ has remarked: "It is an extraordinary fact that some men will not stop smoking even when repeatedly warned that failure to do so will result in the loss of their extremities." At DeWitt General Hospital considerable attention was paid to this "extraordinary fact." What follows may explain, in part, the failure of many soldiers with thromboangiitis obliterans to give up the use of tobacco.

The majority of patients with thromboangiitis obliterans have passed through many medical installations before arriving at one of the vascular centers. When the diagnosis of vascular disorder is first suspected the patient is generally told by the medical officer that he should "stop smoking" or "cut down on tobacco," but the importance of complete and permanent abstinence is not sufficiently stressed. In most instances the patient does originally resolve to stop but subsequently often resumes smoking. With each successive resolution and failure it becomes more difficult for the individual to stop smoking. Horton⁴ quotes Mark Twain to the effect that "he knew all about stopping smoking as he had done it hundreds of times." It is regrettable that many patients with thromboangiitis obliterans are doomed because of their inability to abstain from the use of tobacco.

Rather than to adopt a defeatist attitude toward the problem on the basis that each patient must decide the matter for himself, we have followed the suggestion of Homans,⁷ that "the individual should *know* that he will never smoke again." In order to accomplish this end, the patient is carefully instructed to *keep on smoking* until two objectives are realized: (1) until the diagnosis of thromboangiitis obliterans is irrefutably made and (2) until the patient has had time to consider the matter thoroughly and completely and has come to "know" that he will never smoke again. In other words, the first time that the individual stops smoking is the one time most likely to be successful. The diagnosis of thromboangiitis obliterans must be unquestionable and the patient must be convinced in his own mind of the necessity of stopping. Time is required for both of these facts to be established. As soon as there is no alternative but to stop, the patient quickly adapts himself to the inevitable.

During the earlier period of total abstinence, it has been found helpful to use various types of adjuvants, such as sedatives, occupational therapy, and especially group suggestion. The patients receive considerable help from being segregated into a nonsmoking ward where they are given special privileges.

Under this aggressive policy the proportion of patients who have successfully stopped smoking, at least temporarily, has greatly increased. Of thirty-nine successive cases on the Medical Vascular Section at DeWitt General Hospital, there were only two patients who failed: a 92 per cent success. Much, of course, depends upon the personal relationship between patient and medical officer. Horton⁴ estimates that, of those who stopped smoking, 50 per cent resumed the habit. It is unfortunately likely that many of our patients will return to the use of tobacco after separation from the service.

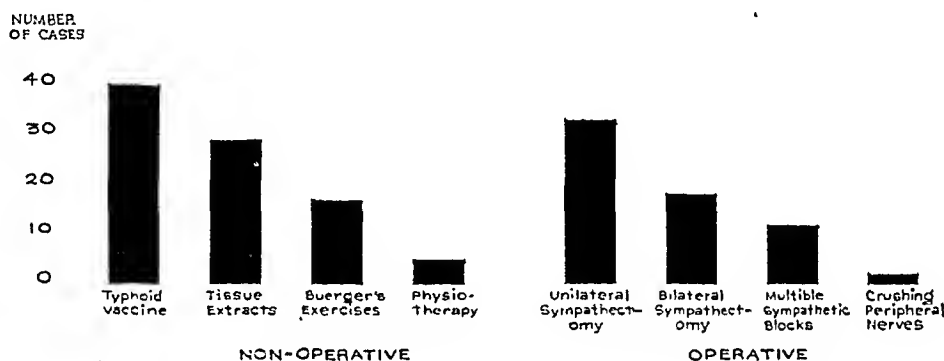


Fig. 6.—Forms of treatment in patients with thromboangiitis obliterans.

The various forms of medical and surgical treatment used in patients with thromboangiitis obliterans are summarized in Fig. 6. Therapy was divided into operative and nonoperative.

Nonoperative Treatment.—*Typhoid vaccine* was administered intravenously in amounts just sufficient to produce malaise with moderate fever (up to 102°F.) but not enough to cause a chill. Provided that the patient had entirely stopped smoking, excellent results were obtained from this method of therapy.

Tissue extracts including Padutin, Depropanex, and pancreatic tissue extracts were injected by the intramuscular route with improvement in ability to walk in 50 per cent of the patients.

Buerger's exercises and *physiotherapy*, including intermittent suction and pressure and intermittent venous occlusion, were employed in numerous cases but the results were not striking.

Operative Treatment.—*Sympathectomy* was the treatment of choice in selected cases. Thirty-three of the 160 patients with thromboangiitis obliterans were subjected to unilateral operation; in eighteen patients bilateral resection of the sympathetic ganglia was performed. Sympathectomy of three extremities was done in two of the patients.

Selection of patients for sympathectomy was made on the basis of clinical evidence of increased vasomotor tone and the response of the blood vessels to temporary inhibition or paralysis of vasomotor tone following sympathetic block or spinal anesthesia. In twelve patients treatment consisted in repeated

blocking of the lumbar sympathetic ganglia with procaine. Crushing of the peripheral nerves for the relief of intractable pain was employed in only two patients.

Good results followed sympathectomy at each of the centers. Ulcers healed, there was relief of rest pain, and the patient's ability to walk was improved. Of thirty-four patients reported from two of the centers, failure to improve was noted in only three patients. Amputation of the leg was necessary in two of these patients. It is significant that all three of these patients continued to smoke. Minor amputations were performed in twelve of the remaining 31 patients.

Disposition.—Only three patients in this series were returned to general duty. An additional twenty-one were sent back to limited duty. The remainder were separated from the service either by retirement or by certificate of disability for discharge.

DISCUSSION

The fact that thromboangiitis obliterans was generally observed in the vascular centers in its earlier stages may have been due to the fact that individuals suffering from disorders of the peripheral circulation, especially those that would interfere with marching, were excluded at the original physical examination. Jahsman and Durham⁸ have reported on the recognition of thromboangiitis obliterans in draftees. It is therefore probable that in most cases in this series the disease commenced during the period of service in the Armed Forces. No evidence was obtained that military service aggravated the condition. The greater awareness of the medical officers during World War II of the problem of vascular disorders of the extremities and the existence of vascular centers where special diagnostic and therapeutic measures were available made for earlier recognition of thromboangiitis obliterans. The small number of cases in which a major amputation of the extremity was necessary casts a more hopeful light on the therapy of this condition.

SUMMARY

The diagnosis of Buerger's disease, thromboangiitis obliterans, was made in 274 of 3,778 patients admitted to the vascular centers of the United States Army General Hospitals. Except for the fact that the condition was generally seen in its earlier stages, its manifestations were not essentially different from those observed in civilians. Intermittent claudication was the initial symptom in two-thirds of the patients. The average duration of symptoms before admission was 21.9 months. All the patients were men and only 20 per cent were of the Jewish race. The diagnosis was made in seven Negro patients. Ninety-two per cent of the cases were in the age group of 26 to 40 years. Blood vessels in two or more extremities were found to be involved in 62.5 per cent of the patients. Oscillometry and the measurement of skin temperatures in a constant temperature room after blocking the sympathetic vasoconstrictor impulses helped in making the diagnosis and in planning treatment. Chief emphasis was placed on complete

abstinence from smoking. Sympathectomy was the treatment of choice in those cases which gave clinical evidence of increased vasomotor tone. Good results were obtained, but only in those patients who abstained completely from smoking.

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THE INFLUENCE OF VITAMIN B₁ DEFICIENCY ON THE PYRUVATE EXCHANGE OF THE HEART

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THE normal heart absorbs both glucose and lactate from the blood stream,¹ substances that must finally be oxidized or converted to glycogen. The influence of the heart on pyruvate, the precursor of lactic acid, has not been studied. It is generally accepted that thiamine is necessary for the utilization of carbohydrate, because that vitamin is required for the oxidation of the carbohydrate split product, pyruvate. In vitamin B₁ deficiency, therefore, pyruvate accumulates and lactate does so even to a greater extent, frequently in a definite ratio to pyruvate.² It has been generally assumed that hyperpyruvemia is a result of a decreased ability of all tissues of the body to utilize pyruvate. In the present investigation, the pyruvate exchanges of the heart were examined in animals suffering from vitamin B₁ deficiency and compared with observations made on the heart of adequately nourished animals.

METHOD

Two groups of dogs were studied: the first was maintained on an adequate diet before the cardiac pyruvate exchanges were determined; the second was fed a mixture containing all known elements required to form a complete diet with the exception of vitamin B₁.² The cardiac metabolism in the second group of dogs was examined in different stages of thiamine depletion, as indicated by presence of neurological or other earlier avitaminotic changes, such as gastrointestinal disturbances. For both groups the final experimental procedures were the same. Each dog was anesthetized with pentobarbital and the trachea cannulated. After the animal was placed on artificial respiration, the sternum was split and the pericardium slit to expose the heart. Blood samples were drawn simultaneously from the coronary sinus and the femoral artery. From a 3.0 c.c. syringe, 2.0 c.c. of blood were expressed into ice-cold trichloroacetic acid for pyruvate determinations,³ 1.0 c.c. into Somogyi solution for sugar⁴ and lac-

From the Department of Physiology and Pharmacology, Albany Medical College, Union University. This work was accomplished with the technical assistance of Mrs. Ilse Memelsdorff and Mrs. Ethel Dodge.

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tate determinations.⁵ Arteriovenous differences equal to or greater than 4.0 mg. per cent of glucose, 1.1 mg. per cent of lactate, and 0.12 mg. per cent of pyruvate are considered significant.

Electrocardiograms were taken, using the three standard leads, at the beginning of the experiment with the animals on an adequate diet and again one or two months later before the animals were placed on a vitamin B₁-deficient diet. Further records were made after three weeks of thiamine deficiency and at the time the animals were sacrificed, both before and after pentobarbital anesthesia.

RESULTS

In Table I are presented the number of observations in which the heart added pyruvate, lactate, and glucose, made no significant changes in their levels, or absorbed these substances from the blood stream. The results are subdivided under three headings: those obtained in the animals on adequate diet, B₁-deficient animals examined before neurological signs developed, and B₁-deficient animals with acute neurological signs. The influence of the heart on the pyruvate exchanges is brought out even more clearly in Table II, in which the first column shows the average of all observations in which pyruvate was absorbed by the heart and the second column shows the average quantity liberated from the heart. The third column presents the average effect for all observations and

TABLE I. EFFECT OF HEART ON PYRUVATE, LACTATE, AND GLUCOSE IN CORONARY CIRCULATION

	HEART		
	ADDED (+)	NO CHANGE (0)	ABSORBED (-)
<i>A. The Normal Exchanges of the Heart</i>			
Pyruvate	1	8	12
Lactate	2	4	7
Glucose	6	5	7
<i>B. Cardiac Exchanges in Vitamin B₁ Deficiency With Neurological Signs</i>			
Pyruvate	18	7	1
Lactate	3	6	15
Glucose	7	10	7
<i>C. Cardiac Exchanges in Vitamin B₁ Deficiency Before the Development of Neurological Signs</i>			
Pyruvate	0	0	11
Lactate	0	0	11
Glucose	2	5	4

(+) Number of observations in which substance was added to blood; (0) number in which there was no significant change; and (-) number in which substance was absorbed by the heart.

TABLE II. CARDIAC PYRUVATE BALANCE

	ADDED (+)	ABSORBED (-)	BALANCE*
Normal	0.21 (1)	0.72 (12)	-0.66 (13)
No neurological signs	0.00 (0)	0.82 (11)	-0.82 (11)
Neurological signs	0.51 (18)	0.26 (1)	+0.47 (19)

Figures in parentheses indicate number of observations.

(+) Average of all observations in which pyruvate was added to the blood stream; (-) average of all observations in which pyruvate was absorbed by the heart.

*Average of all significant observations.

shows that the normal heart absorbs pyruvate. The heart of animals exhibiting acute neurological symptoms poured pyruvate more consistently than lactate into the blood stream. On the other hand, the heart of dogs which did not show neurological lesions, with one exception, revealed a picture closely allied to that of the normal animal. The one exception was an animal given 2.0 mg. of thiamine intramuscularly when symptoms of acute vitamin B₁ deficiency were precipitated. This dose did not reverse the neurological signs, although it was adequate to cause the heart to absorb pyruvate from the blood.

In regard to the correlation of electrocardiographic findings with pyruvate balance and neurological signs, the following statements may be made: (1) In the two dogs which did not show acute neurological signs nor any reversal of the normal cardiac pyruvate balance, the electrocardiograms remained essentially unchanged except for variations in rate. (2) In five dogs exhibiting pyruvate output by the heart, there were definite T-wave changes in the electrocardiogram, the T wave being either inverted or diphasic. These five dogs all showed definite neurological signs. In one dog with diphasic T waves, the pyruvate results were not conclusive and neurological changes were absent. (3) Three dogs had definite T-wave changes and neurological alterations, but biochemical studies were not obtained.

DISCUSSION

The present observations not only confirm for the normal heart the absorption of glucose and lactate from the blood stream, but reveal that pyruvate is also extracted from the coronary blood. The heart possesses a greater blood supply than skeletal muscle and accordingly receives more oxygen per weight of muscle. That organ, therefore, not only oxidizes all the carbohydrate split products formed within it, but also utilizes some poured into the blood stream by other organs. The present theories of carbohydrate metabolism postulate that pyruvate, formed according to the Embden-Meyerhof scheme from the breakdown of glycogen to pyruvic acid, is oxidized to water and carbon dioxide with the catalytic aid of vitamin B₁.⁶ In a thiamine-deficient animal, the heart loses the ability to oxidize pyruvate and that substance, along with lactate, its reduced form, accumulates in the blood stream. Unlike the effect of vitamin B₁ deficiency on the pyruvate balance of liver, intestine, and skeletal muscle,⁷

in the heart a reversal of the normal pattern occurs. In view of the different actions observed in the heart and other organs, it would seem that an important source of the hyperpyruvemia observed in vitamin B₁ deficiency is the heart.

This cardiac effect has clinical significance, especially when we recall that, at least in the present observations, the appearance of neurological signs was accompanied by an outpouring of pyruvate from the heart. The influence of this abnormal metabolism is observed not only functionally in the changes in the electrocardiogram and the dilated heart, but may also be accompanied by morphologic alterations.⁸ It is interesting that cardiac failure is also associated with an abnormally high pyruvate concentration in the blood⁹ and that the heart in experimental coronary occlusion releases lactate into the blood stream.¹⁰

No electrocardiographic changes of any significance were noted before the dogs showed definite neurological signs of vitamin B₁ deficiency. After these signs were exhibited, the electrocardiograms did contain changes involving mainly the form of the T wave. Since an outpouring of pyruvate was found to be associated with T-wave changes, the cardiac pyruvate metabolism may be one of the factors determining the T-wave form. These observations suggest that for the minor unexplained T-wave changes commonly found in clinical cases, the possibility of a thiamine deficiency must be considered.

SUMMARY AND CONCLUSIONS

Five dogs were studied for the normal cardiac exchanges of pyruvate, lactate, and glucose and eleven animals with vitamin B₁ deficiency were examined. In most instances pyruvate was removed from the blood in the normal animal and also in animals without neurological lesions. In the latter, the removal was even more marked, perhaps because of the higher level of pyruvate in the arterial blood. In the animals with neurological symptoms, the heart poured additional pyruvate into the blood stream despite the hyperpyruvemia. The inability of the heart to absorb pyruvate is, therefore, one of the factors increasing the pyruvate level in the blood in vitamin B₁ deficiency.

Many of the animals with vitamin B₁ deficiency exhibited T-wave changes. These alterations in the form of the T wave were usually associated with an outpouring of pyruvate from the heart and occurred most consistently in animals which exhibited neurological signs. These observations lead to the suggestion that in patients who exhibit T-wave abnormalities, vitamin B₁ deficiency should be suspected as an etiologic factor.

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PATHOLOGY OF THE MITRAL VALVE IN THE OLDER AGE GROUPS

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ABNORMALITIES of the mitral valve are frequently encountered in necropsies of elderly subjects. In the earlier decades of life, the interpretation of these lesions is not difficult. In older individuals, however, there is frequent difficulty in explaining their pathogenesis. In the younger groups, the pathologic changes are usually the result of inflammatory lesions, while in the older groups the origin of the old scarred and degenerative processes which are found is not always apparent. Pathologists are frequently asked whether a given lesion in the mitral valve is of rheumatic or arteriosclerotic origin. This question presupposes that there are rigid criteria for differentiating these changes and fails to take cognizance of the fact that, in the older age groups, degenerative lesions are not infrequently superimposed upon inflammatory ones. The differentiation of these two types of lesions has its limitations even microscopically.

In order to survey the types of lesions in the older age groups, we selected 200 consecutive necropsies performed upon patients at Goldwater Memorial Hospital. This is a hospital for chronic diseases and the large majority of our patients fall into the older age groups. We wish to emphasize that our figures refer only to the patients in this hospital and probably do not have any statistical bearing upon the occurrence of mitral lesions in the general population, since the proportion of patients with cardiovascular disease in this hospital is large. An attempt was also made to correlate the pathologic material with the clinical records.

CRITERIA

For the purpose of our study, each of the valves was placed in one of the following categories:

- I. Normal valves
- II. Abnormal valves without evidence of inflammatory changes
- III. Abnormal valves of inflammatory origin
 - A. Nonrheumatic
 - B. Rheumatic
 1. Acute
 2. Chronic
 3. Healed

Normal Valves.—A valve was considered normal if the leaflets were thin and flexible, the chordae thin and delicate, and the ring of normal size and consistency. Some valves whose leaflets were described as "slightly thickened" were also placed in this category. Since no absolute standard exists for the normal thickness of a valve at any age, it was felt preferable not to draw too fine a conclusion from the gross appearance of a valve regarding its deviation from the normal. Gross and Kugel¹ found that, with advancing age, progressive changes, including collagenous and elastic thickening, develop in the valves of the heart. This factor must be considered when dealing with heart valves of patients in the older age groups.

Abnormal Valves Without Evidence of Inflammatory Changes.—This term was used to describe those valves which were considered abnormal but which failed to show microscopic evidence of inflammatory change. Generally the involvement was more of the ring region than of the valve itself. The valve leaflets varied in appearance. Sometimes they were delicate, but more often they showed some thickening or deposition of atheromatous material. In the ring region, the atheromatous material was nodular, although occasionally it was found to involve the entire base of the valve and to form a ring at the orifice. Sometimes the foreign material was obviously calcific. In most cases, no appreciable narrowing of the valve orifice was seen, but in two cases an actual stenosis was found. Microscopically, collagen thickening, hyalinization, lipoid deposition, and calcification were frequently encountered.

Strictly speaking, a congenitally abnormal valve would be placed in this category. We had only one case in which this consideration arose. This was the case previously described by us under the title of "The Tetralogy of Fallot."¹¹ Case 1 This patient had a congenital abnormality of the pulmonic valve which subsequently was involved by a rheumatic process. The mitral valve which showed an inflammatory process was not congenitally abnormal, and therefore this case is included in the rheumatic series.

Abnormal Valves of Inflammatory Origin—Nonrheumatic.—This group would include specific conditions such as acute and subacute bacterial endocarditis, disseminated lupus erythematosus, and terminal endocarditis. Actually, none of our cases were placed in this classification. Accordingly, all valves of our series which showed inflammatory changes were placed in one of the rheumatic categories.

Abnormal Valves Due to Acute Rheumatic Involvement.—Valves placed in this classification showed an acute valvulitis with the presence of acute granulation tissue including fibrin, inflammatory cells, and newly formed blood vessels. These deposits were found in the valve substance itself or, more frequently, they constituted verrucae which projected from the surface of the valve over an underlying valvulitis. Aschoff bodies were only rarely found in the myocardium; in general, the inflammatory lesion of the valve was not accompanied by a corresponding lesion in the myocardium. The degree of inflammatory response varied but in most cases was not extensive. The acute lesions were all seen in valves which had previously been inflamed.

Abnormal Valves Resulting From Chronic Rheumatic Involvement.—This group included those valves which showed inflammatory changes of a chronic nature. The valves were thickened, fibrotic, and hyalinized; some were calcified. The essential change, however, was the presence of a moderate to severe inflammatory infiltration consisting mainly of lymphocytes, diffusely and focally distributed throughout the valve substance, as well as definite vascularization of the valve. The outstanding lesion, therefore, was a persistent cellular inflammatory process.

Abnormal Valves Resulting From Healed Rheumatic Involvement.—The basis for this diagnosis was principally the finding of vascularization and fibrosis of the valve of long standing. A slight cellular infiltration occurring as scattered cells at times accompanied these lesions. The question of the presence of blood vessels in the normal human valve has been considered by many writers.²⁻⁷ The consensus is that blood vessels are not found in the normal human valve on microscopic section. There are still some differences of opinion concerning the value of injection methods for demonstrating vessels in a valve; the majority of pathologists believe that microscopic examination is superior to the injection method. When vessels are present in a valve and show, in addition, irregularity and thickening of their walls, irregularity of their lumens, perivascular fibrosis, and cellular increase in their vicinity, their inflammatory origin is assured. Since vascularization of the mitral valve occurs in only a few specific conditions other than rheumatic disease and since these are not applicable to our cases, we have considered all vascularization to be an indication of rheumatic involvement of the valve. The only exception made was for the finding of a few vessels in the proximal portion of the valve where there was extension into it of the auricular myocardium. When found in a sclerotic valve, such vessels were not considered to be abnormal, even if their walls were slightly thickened; it was assumed that such sclerosis had occurred simultaneously with a comparable process in the valve and was not due to an antecedent inflammatory process. The presence of blood vessels alone was considered to be significant only if the vessels were found in the valve proper; the finding of a few vessels in the valve ring was not considered to be diagnostic of an inflammatory process. Had we included these latter instances in our rheumatic series, our figures would have been higher than they are. The microscopic appearance of the other valves was occasionally taken into consideration in those borderline cases where the differentiation was difficult, as was the appearance of the pericardium and the auricular endocardium. Generally, however, each valve was evaluated on the basis of its own appearance.

It is in healed rheumatic valves particularly that a degenerative process, consisting of hyalinization, atheroma, and calcification, may be superimposed and may mask the original disease. Careful attention to the microscopic picture, however, will usually show the underlying ancient inflammatory process. Vague outlines of hyalinized blood vessels merging into the general fibrous mass may sometimes be seen. Some information may be obtained from the fibrosed tissue itself. Hyalinized fibrous tissue of inflammatory origin is more of a true scar

and its bundles are more likely to assume a crisscross arrangement, whereas fibrosis due to simple collagen condensation is more likely to be linear. It must also be pointed out that in some instances of healed rheumatic endocarditis, all traces of a former inflammatory process may have disappeared and only a thickened fibrotic valve may remain.

MATERIAL

Of the 200 consecutive autopsies studied, twenty-three were unsuitable either because of insufficient data or because the patients were below the required age of 40 years which we had set as the lower age limit. The remaining 177 cases furnished the material for our analysis.

The classification of the mitral valves of the 177 cases is shown in Table I.

TABLE I. LESIONS OF THE MITRAL VALVE

I. Normal valves					96
II. Abnormal valves without evidence of inflammatory changes					49
III. Abnormal valves of inflammatory origin					32
A. Nonrheumatic					0
B. Rheumatic					32
1. Acute					7
2. Chronic					8
3. Healed					17

	MALE	FEMALE	TOTAL	%
Normal	68	28	96	54
*Abnormal	44	37	81	46
Total	112	65	177	

*ABNORMAL VALVES

Rheumatic	15	17	32	40
Nonrheumatic	29	20	49	60
Total	44	37	81	

Age and Sex.—The total percentage of abnormal valves was approximately the same in each age group (Table II). This may be explained by the fact that there were relatively more rheumatic valves in the younger age groups and relatively more atherosclerotic valves in the older age groups. There is a tendency for the percentage of rheumatic valves to decrease with advancing years. The persistence of a considerable percentage of rheumatic valves in the older age groups might at first seem strange. However, these figures relate to the finding of any signs of rheumatic involvement even though the inflammatory process may have become healed. The peak of deaths due to rheumatic heart disease

TABLE II. AGE AND SEX OF 177 PATIENTS WITH ABNORMAL MITRAL VALVES

	40-49 yr.			50-59 yr.			60-69 yr.			70-79 yr.			80-89 yr.			90-99 yr.			TOTAL		
	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL
Rheumatic	1	4	5	4	6	10	4	3	7	3	4	7	3	0	3	0	0	0	15	17	32
Nonrheumatic abnormal	0	2	2	4	2	6	11	6	17	8	4	12	8	3	11	0	1	1	31	18	49
Total abnormal	1	6	7	8	8	16	15	9	24	11	8	19	11	3	14	0	1	1	46	35	81
Normal	6	3	9	14	6	20	21	10	31	15	6	21	11	2	13	2	0	2	69	27	96
Total	7	9	16	22	14	36	36	19	55	26	14	40	22	5	27	2	1	3	115	62	177
Per cent rheumatic			31			28			13			17.5			11			0	13	27	18
Per cent total abnormal			43.5			44.6			46			47.5			52			33	40	51	46

was in the fifth decade, but the number of deaths in the sixth decade was not much lower. There were instances of active inflammatory processes even in the eighth decade.

ABNORMAL VALVES WITHOUT EVIDENCE OF INFLAMMATORY CHANGES

In forty-nine (27 per cent) of our series of 177 patients, the abnormalities of the mitral valves were considered to be the result of noninflammatory changes. The findings varied from slight thickening to manifest atheroma and calcification. In the large majority, there was fibrosis and hyalinization of the ring region and, to a lesser extent, of the valve itself. Patchy deposits of lipid material and small honeycombed areas of vacuolization were found.

Generally, the more deformed valves were of inflammatory origin, while those with ring calcification or atheroma were the result of noninflammatory processes. Of interest is the fact that in the entire series, mitral stenosis was found in fourteen patients. In twelve of these the lesions were the result of rheumatic disease and in only two were they considered to be of noninflammatory origin. A brief description of the latter two cases follows:

Case 362, a man, 72 years of age, died as a result of hepatoma and portal cirrhosis. There was a narrowing of the mitral orifice due to fibrosis and calcification of the mitral ring which was hard, rough, and apparently atheromatous. The chordae tendineae were delicate. The left auricle was moderately dilated. No microscopic evidence of rheumatic involvement was present.

Case 287, a 73-year-old woman, died of bronchopneumonia and hypertensive heart disease. The mitral opening was reduced, the ring was thickened and atheromatous, and the leaflets were slightly thickened. The chordae tendineae were delicate. The left auricle was not dilated. No microscopic evidence of rheumatic involvement was present.

THE RHEUMATIC VALVES

There were thirty-two patients (fifteen men and seventeen women) in whom the etiology of the changes in the mitral valve was considered to be rheumatic disease (Table III). Among these the mitral valves of twenty-nine showed various degrees of thickening of the valve, or of the ring, or of both. In twelve of the thirty-two patients there was definite mitral stenosis (Table IV) and in eighteen combined mitral and aortic lesions. The changes in the aortic valves varied from thickening and slight atheromatosis, which occurred in most of the cases, to aortic stenosis which was present in three patients. In seven patients of the rheumatic series, the mitral lesions were accompanied by tricuspid lesions.

Most of the rheumatic valves showed the usual findings of rheumatic endocarditis, including thickening and shortening of the valve leaflets with rolling of the edges. Old atheromatous nodules as well as recent verrucae were described. Shortening of the chordae tendineae and fibrosis of the adjacent endocardium were observed in most of the cases. Calcification was a frequent finding. Fibrous and atheromatous plaques were mentioned in several instances. Where mitral stenosis was present, the valves were thickened, fibrotic, and narrowed. In the hearts of six patients in whom mitral stenosis was present, there was gross

TABLE III. ANALYSIS OF THIRTY-TWO PATIENTS IN WHOM THE ETIOLOGY OF THE VALVE LESION WAS RHEUMATIC DISEASE

CASE NO.	AU-TOPSY SEX	AGE	HIS-TORY	MURMURS	CROSS DESCRIPTION OF VALVES			MICROSCOPIC DESCRIPTION OF MITRAL		
					MITRAL	TRICUSPID	AORTIC	RING	PROXIMAL	DISTAL
1	206	M	69	0	T, Ver.			H—Mod., V—Occ.	H—Mod., V—Mod.	H—Mod., V—Mod., C—Sl.
2	220	F	53	BS	T, St.	T	Ca., a	H—Mod., V—Occ.	H—Mod.	H—Mod.
3	221	M	87	AS, BS	T		a, T	Ca.—Mod, V—Mod., C—Mod.	V—Occ., C—Occ.	V—Mod, C—Mod.
4	222	F	60	AS	T, St., Ca		a	H—Mod.	H—Sl., V—T	V—T, Mod.
5	239	M	53	AS, AD	T St., Ca	T	a	C—Mod., V—Mod.	C—Mod.	H—Mod.
6	241	F	71	AS	T Ca.	T	a	Ca.—Mod., V—Mod.	V—Mod.	H—Mod.
7	245	F	57	AS, AD	T, St.	T	T	C—Mod., V—Mod. T	V—Mod., C—Mod., Ca.—Mod	V—Mod., C—Marked
8	257	M	74	0	T			C—Mod.	C—Mod., V—Mod.	V—Mod., C—Mod.
9	260	F	75	AS, BS	T Ca.		T, Ver.	V—Mod. T	V—Occ.	H—Mod.
10	263	F	54	AS	T St., Ca.		T	Negative	V—Mod., C—Mod.	Negative
11	266	F	62	0	T St.		a, T	H—Mod., V—Mod.	V—Mod., C—Mod.	V—Few, C—Few
12	271	F	42	AS, AD	T, St., Ca.		T, a	V—Mod., C—Mod., Ca.—Mod	V—Mod, C—Mod.	V—Mod., C—Mod.
13	272	F	62	AS	T St.		T, a	Ca.—Mod, V—Few	V—Mod. T	V—Mod., T
14	276	M	78	AS, AD, BS	T		T a	V—Mod, C—Mod., F—Mod.	V—Mod., C—Mod.	V—Mod., C—Mod.
15	279	M	41	AS, AD, BD	T, Ver.		T a	C—Few, V—Mod.	C—Mod, V—Mod.	C—Mod., V—Mod.

16	280	F	52	+	AS	T				H—Mod., V—Mod.	V—Mod., H—Mod., Ca.—Mod	H—Mod., V—Sl.
17	285	F	59	—	AI, BS	T, Ca.				Ca.—Mod., V—Many T	V—Mod., C—Few	F—Mod., V—Mod., C—Few
18	307	M	62	—	0	T				V—Few	V—Many, C—Few	V—Mod., C—Few
19	309	F	40	—	MS	T				C—Mod., V—Sl.	C—Few	
20	314	F	59	—	0					V—Mod., C—Mod.	V—Mod., C—Mod.	H—Mod.
21	317	F	42	—	AS, BD	T, St.				C—Few	H—Mod.	V—Few, C—Mod.
22	321	M	85	—	AS, BS	St., Ca.				C—Mod., F—Mod.	V—Few, C—Mod., Ver.	C—Mod., V—Mod.
23	327	M	52	—	AS	T, Ver.				C—Occ.	C—Occ., V—Mod. T	H—Mod., C—Many
24	334	M	65	—	AS				St.	H—Sl., V—Mod.	C—Few, V—Mod. T	H—Sl.
25	340	M	81	—	0	St.			St.	C—Mod., V—Mod.	C—Mod., V—Mod.	C—Occ., V—Occ.
26	343	F	71	—	AS, BS	T, Ca.				V—Mod., Ca.—Mod.	V—Mod., C—Mod.	H—Mod.
27	360	M	53	+	AS, AD, BS, BD				Congenital Pul.	Ca.—Mod., H—Mod.	H—Mod.	H—Mod.
28	373	F	42	+	AS, AD, BS, BD	St.		St.	T, St.	V—Mod., C—Mod.	V—Mod., C—Mod.	V—Mod., C—Mod.
29	374	M	69	—	0	T, Ver.			T	Ca.—Mod., V—Few	Ca.—Mod., V—Mod.	C—Mod., V—Mod.
30	377	M	50	—	0					V—Mod. T.	V—Sl. T	H—Mod., V—Mod. T
31	378	F	79	—	AS	T				H—Mod., V—Mod.	H—Mod., V—Mod.	H—Mod., V—Mod. T
32	381	M	73	—	0	T				V—Many, H—Sl., Ca.—Mod.	H—Mod., V—Mod.	H—Sl., V—Many T, C—Sl.

0, None; BS, basal systolic; BD, basal diastolic; AS, apical systolic; AD, apical diastolic; MI, mitral insufficiency; MS, mitral stenosis; AI, aortic insufficiency; T, thickened; Ver., acute verrucae; Ca., calcification; a, atheroma; H, hyalinization; F, fibrosis; V, vessels; C, cells; Sl., slight; Mod., moderate; Occ., occasional; St., stenosis.

TABLE IV. DESCRIPTION OF THE MITRAL VALVES IN NINE PATIENTS WITH RHEUMATIC MITRAL STENOSIS

NO.	CASE	AGE	SEX	TYPE OF LESION
1	222	60	F	Thickened, calcified valve
2	239	53	M	Thickened, calcified valve
3	245	57	F	Thickened, rolled
4	263	54	F	Thickened, atheromatous, calcified
5	266	62	F	Thickened, atheromatous
6	272	62	F	Thickened, calcified
7	317	42	F	Thickened, fibrotic
8	321	85	M	Fibrotic, calcified
9	340	81	M	Fibrotic, calcified
10	373	42	F	Thickened, rolled
11	220	53	F	Thickened, rolled, calcified
12	271	42	F	Thickened, calcified

calcification. It is of interest that nine of the twelve patients with mitral stenosis were women.

In three patients of this series, the valves were described as being normal on gross examination, but an inflammatory lesion was found microscopically. A brief description of the three cases follows:

Case 314, a 59-year-old woman, died of fat embolism following a bone fracture. The mitral valve showed interstitial valvulitis. The myocardium showed Aschoff bodies.

Case 334, a man, 65 years of age, died of carcinoma of stomach. The mitral valve showed thickened blood vessels and a moderate cellular infiltration in the proximal portion. The aortic valve showed aortic stenosis of moderate degree with fusion of the commissures.

Case 377, a 50-year-old man, died from rheumatoid arthritis and amyloid disease. Both the mitral ring and mitral valve showed a moderate number of vessels which were thickened and merged into a fibrotic valve structure.

Activity of Rheumatic Disease.—In a practical consideration of rheumatic disease of the heart, the question of the presence or absence of activity will arise. Activity is a clinical rather than a pathologic term, although evidence of clinical activity frequently can be substantiated morphologically. Thus, the finding of an acute pathologic lesion characterized by the presence of masses of inflammatory cells and particularly polymorphonuclears, fibrin, or necrotic tissue is evidence of an active process. However, the point at which clinical activity ceases is not one that can be precisely defined histologically. Thus, lymphocytes are seen for a long time in tissues which have no demonstrable evidence of inflammatory activity clinically, as, for example, in arrested tuberculous foci. The same may be true of rheumatic valvular disease. One cannot judge, therefore, the exact clinical response from the observation of the number of cells seen in a lesion; one can merely arrive at some opinion regarding the acuteness or chronicity of the disease from seeing the numbers and types of cells in the lesion. The converse, however, is true; when all inflammatory cells have disappeared, the lesion is undoubtedly inactive.

In the view of the foregoing considerations, we examined the thirty-two cases designated as rheumatic for the presence or absence of cells in the mitral valve, as well as for the finding of a superadded acute inflammation (Aschoff bodies, verrucae, etc.).

In seventeen cases (53 per cent) of the rheumatic series, the mitral valve was in a healed or scarred state. In fifteen (47 per cent), a cellular inflammatory response of varied degree was present. Generally, the cellular collections were not marked and were of the type seen in a chronic, mild, valvulitis. Vascularization and sometimes calcification accompanied the cellular collections. The cells were chiefly lymphocytes, although histiocytes and fibroblasts were frequently seen. Table V indicates the approximate degree of this involvement.

Among the fifteen patients in whom a cellular reaction was present, there were seven which showed evidence of a more acute lesion.

Case 206, a man, 69 years of age. The mitral valve showed recently organized verrucae.

Case 245, a woman, 57 years of age. The mitral valve showed an extensive cellular infiltrate which contained numerous polymorphonuclear leucocytes.

Case 279, a man, 41 years of age. The mitral valve showed extensive acute valvulitis and recent organizing verrucae.

Case 314, a 59-year-old woman. The mitral valve showed moderate vascularization. The myocardium showed several Aschoff bodies in the vicinity of blood vessels.

Case 327, a 52-year-old woman. The mitral valve showed recent organizing verrucae.

Case 374, a 69-year-old man. The mitral valve showed recently organized verrucae with palisading.

Case 360, a 53-year-old man, died in congestive heart failure. The basic heart lesion was congenital, the Eisenmenger complex. There was also evidence of rheumatic involvement of the mitral and pulmonic valves. The myocardium showed Aschoff bodies.

Accordingly, it can be said that the presence of an inflammatory cellular response was found in 47 per cent of the rheumatic series and that in 22 per cent there was evidence of a more acute lesion; or, more simply, slightly less than one-half of the thirty-two patients with rheumatic disease showed a cellular inflammatory lesion of the mitral valve of varied degree and slightly less than one-quarter showed acute lesions. In two of the latter, in addition to valvulitis, Aschoff bodies were demonstrated in the myocardium.

History of Rheumatic Fever.—Of the thirty-two patients with rheumatic mitral disease, a positive history of rheumatic fever was elicited in only five (Table VI).

A negative history of rheumatic fever in patients in the older age groups is therefore of little help in diagnosis. Of especial interest is one patient (Case 260) who gave a history of "rheumatism" lasting for sixty days at the age of 29 years and who lived to the age of 75; death was the result of carcinoma of the rectum. A loud systolic murmur was present during life. At autopsy was shown deformity of the mitral valve with thickening and nodularity of the mitral leaflets and with chordae tendineae which were shortened and thickened and which bound down the valve.

TABLE V. FINDINGS IN PATIENTS WITH INFLAMMATORY CELLULAR CHANGES OF THE MITRAL VALVE

NO.	CASE	SEX	AGE	HISTORY OF RHEUMATIC FEVER	DIAGNOSIS OF RHEUMATIC FEVER MADE	CLINICAL EVIDENCE OF ACTIVITY	PATHOLOGIC EVIDENCE OF ACTIVITY	GROSS LESIONS
1	206	M	69	0	0	0	Recently organizing verrucae	Thickened, verrucae
2	221	M	87	0	0	0	0	Thickened valve and ring
3	245	F	37	+	+	0	Many cells including numerous polys	Mitral stenosis
4	271	F	42	0	+	0	0	Mitral stenosis
5	276	M	78	0	0	0	0	Thickened
6	279	M	41	0	0	0	Recent organizing verrucae, extensive acute valvulitis	Thickened, verrucae
7	314	F	59	0	0	0	Aschoff bodies in myocardium	Normal
8	317	F	42	0	+	0	0	Mitral stenosis
9	321	M	85	0	0	0	0	Mitral stenosis
10	327	M	52	0	0	0	Organizing verrucae	Thickened, calcified
11	340	M	81	0	0	0	0	Mitral stenosis, calcification
12	343	F	71	0	0	0	0	Thickened, calcified
13	360	M	53	+	+	0	Aschoff bodies in myocardium	Pulmonic stenosis, tricuspid insufficiency
14	373	F	42	+	+	0	0	Mitral stenosis
15	374	M	69	0	0	0	Recent organizing verrucae	Thickened, nodular verrucae

TABLE VI

CASE	SEX	AGE AT ONSET	AGE AT DEATH
245	F	24	57
260	F	29	75
280	F	22	52
360	M	25	53
373	F	32	42

The absence of a positive history, therefore, is usual in older patients with rheumatic disease. Patients who died in the fifth or sixth decade are more likely to give a positive history than those who die later. The former constitute a group in which a correct diagnosis is made during life. Many of the others who die at a more advanced age are undiagnosed or are considered to be cases of arteriosclerotic heart disease.

Physical Examination.—A complete analysis of the physical findings in the rheumatic patients was not undertaken. Consideration was given only to the presence or absence of murmurs. Murmurs were present in twenty-three patients (72 per cent) and absent in nine cases (28 per cent). In two of the patients in whom no murmurs were heard, the valves were grossly normal, though microscopic evidence of rheumatic involvement was present. In five patients in whom no murmurs were heard, the valves were grossly abnormal, the leaflets being definitely thickened. In two of these five patients, the lesion was mitral stenosis: one patient had auricular fibrillation throughout his hospital stay; the other patient was on a surgical service with diabetes and gangrene of the leg and only one examination of the heart was recorded. In four of the nine patients in whom murmurs were not recorded, there was cellular infiltration of the mitral valve which suggested a continuing inflammation. It is apparent that the absence of murmurs does not exclude the possibility of rheumatic valvulitis in patients in the older age groups.

Contribution of Rheumatic Valvulitis to Morbidity and Mortality.—The effect of the abnormal valve on the patient's course was considered. This was most difficult to evaluate since many factors were involved. In fifteen of the thirty-two patients in the rheumatic group, the abnormality of the mitral valve was considered to have contributed to the patients' illness and, in some cases, to his death. This conclusion was reached either because the valvular deformity was such that a dysfunction had apparently been present during life, or because the clinical record, as well as the pathologic findings, indicated the presence of an acute lesion, and particularly one which involved the myocardium. Of these fifteen, ten were in Class III-B-1 (acute rheumatic) and III-B-2 (chronic rheumatic), while five were in Class III-B-3 (healed rheumatic). The implication of these figures is that the influence of acute and chronic rheumatic valvulitis upon

morbidity and mortality was more than twice that of healed rheumatic valvulitis. In more than one-half of the total number of patients (seventeen of thirty-two) the rheumatic lesion was not of clinical significance.

CALCIFICATION

In considering the frequency of rheumatic endocarditis in the older age group, one eventually must face the problem of the atheromatous and calcific valve. That the finding of calcium is not a rarity can be seen from the fact that we found calcific deposits in the mitral valve in 30 per cent of our patients. The deposits were, in some instances, large and easily palpable. In some specimens the deposits encircled the entire valve base; in others they were felt as nodular collections either in the valve ring or in the valve proper; and in still other instances, the calcium was demonstrated only by microscopic study. Our figures for the presence of calcium are undoubtedly too low, since only one or, at most, several sections of the valve were available for study. Whether such deposits are merely an infiltration into the tissue of the valve of extraneous material due to local metabolic disturbances or whether they are the end results of an inflammatory process is a differentiation which is difficult to make on gross examination and not always possible even on microscopic examination. The problem is all the more difficult since we found deposits of calcium without any inflammatory reaction in their vicinity in valves which showed typical rheumatic disease in adjacent portions, while on the other hand we found blood vessels and sparse numbers of lymphocytes around deposits of this material in the valve ring in valves which otherwise showed no signs of rheumatic endocarditis. That calcium by itself does not produce any inflammatory response is seen from the fact that we have seen numerous instances of calcium deposit in heart valves without any accompanying inflammatory reaction whatever. This view has been expressed by Clawson and co-workers.⁸

The deposition of calcium is apparently part of the healing process in rheumatic disease. We have seen well-formed calcium deposits in the valve of a girl of 13 years who died of rheumatic endocarditis. Consequently, one has to bear in mind that the finding of calcium does not necessarily indicate a degenerative lesion alone. In many cases it undoubtedly indicates the end result of a rheumatic process.

Types of Calcium Deposition.—Examination of the valves reveals that calcium is to be found in three well-discernible forms:

1. A granular or dustlike infiltration. This is most frequently seen in the valve proper, although it may occur also in the ring. It is not accompanied by any blood vessel or cellular increase. Occasionally, however, the outlines of blood vessels may be found; the processes appear to be unrelated. This type of calcific deposition is found usually in the valves of old patients.

2. Patches of calcific material in the valve ring sometimes extending for a short distance into the valve itself and sometimes accompanied also by calcification of the adjacent ventricular myocardium. The material appears as sheetlike

deposits. It merges with the adjacent more normal tissues and appears merely to replace tissue that had been previously damaged. Blood vessels do not accompany this type of lesion. Occasionally, such deposits are seen also in the valve proper. These lesions appear to be noninflammatory in origin, although we have seen them in valves that showed definite evidence of a previous rheumatic disease.

3. Patchy deposition in multilocular or honeycombed spaces, accompanied by either blood vessels or cells, or both, and located usually in the valve ring and not infrequently in the valve proper. Such deposits in the valve or ring and accompanied by old granulation tissue are characteristic of healing rheumatic endocarditis. However, we have seen a considerable number of such deposits limited to the ring and fringed by blood vessels, which usually appear to be dilated capillaries, in valves which otherwise showed no evidence of an old inflammation. Occasionally, small numbers of lymphocytes are seen in the vicinity. While we have been suspicious of the possible inflammatory origin of these latter lesions, we have nevertheless not considered such lesions which are limited entirely to the mitral ring as being sufficiently definite to warrant their classification as rheumatic.

We found calcification in fifteen of the thirty-two rheumatic patients (47 per cent) and thirty-eight of the 145 nonrheumatic patients (26 per cent). In ten of the fifteen rheumatic patients, calcification was noted grossly (as well as microscopically), while in five the deposits were seen only on microscopic study. In the thirty-eight nonrheumatic patients, calcification was seen grossly in five, while in thirty-three patients it was demonstrated only microscopically.

To summarize, therefore, calcification with or without vascularization is frequently seen in old rheumatic endocarditis. The multilocular type described is more likely to be of rheumatic origin and to be accompanied by vascularization, lymphocytic infiltration, and fibrosis. Nevertheless, if it is limited to the ring region and is not accompanied by a definite valvulitis, it cannot be assumed to be definitely of rheumatic origin.

DISCUSSION

Lesions of the mitral valve occur with considerable frequency in the older age groups. In our hospital population, 45 per cent of the patients analyzed showed some abnormality of the mitral valve. Such lesions of the mitral valve are either of inflammatory or of noninflammatory (degenerative) origin. At times, degenerative changes may be superimposed upon originally inflammatory lesions. In patients over 40 years of age, rheumatic lesions of the mitral valve are not rarities. In the total series of 177 patients over 40 years of age, such lesions were present in 18 per cent.

In 47 per cent of the rheumatic series, a cellular inflammatory process was demonstrated in the mitral valve. The more extensive and deforming lesions of the mitral valve are, in the large majority of cases, of rheumatic origin: This etiology is especially suggested if the involvement includes the valve leaflets. Cellular reaction, when present, varies in degree. At times it is not marked, but

occasionally it may be accompanied by verrucae and rarely may be associated with Aschoff bodies in the myocardium. The presence of such inflammatory lesions is not limited to any particular age group. Four patients whose valves showed inflammatory lesions were, respectively, 78, 81, 85, and 87 years of age.

The presence of calcification in a valve does not necessarily indicate a degenerative etiology. Fifteen of our rheumatic patients showed calcification and six of nine of our patients with rheumatic mitral stenosis showed the presence of calcium. Calcium by itself does not produce an inflammatory reaction. When calcification is found in the valve proper and is accompanied by blood vessels, inflammatory cells, or both, it is a consequence of an inflammatory process. When calcification is limited to the mitral ring alone and is not accompanied by other evidences of a preceding inflammatory process, a definite rheumatic etiology cannot be assumed.

The rheumatic process is thus long and protracted and not necessarily limited to youth, although its greatest incidence and its most spectacular phases occur then. Cohn and Lingg,^{9,10} in their clinical analysis of 12,000 cases, have spoken of an active phase and of a latent phase. The pathologic analysis of our small group of cases agrees with this view. The latent phase may extend for months, or for a great many years, as was the case in some of our patients. The belief that the disease can exist for a short time and be entirely eradicated may be true in some instances. On the contrary, the process may linger on for a long time and be subject to minor exacerbations of which the patient is unaware. Inflammatory foci may apparently become active in a valve without being accompanied necessarily by myocardial lesions. In other instances, the healed lesion may remain for a long time, with or without physical findings, and without shortening the patient's life. Thus, in our series, seventeen patients (53 per cent) with rheumatic disease were more than 60 years of age at the time of their death and three were more than 80 years of age. Most of the patients in this series did not die of rheumatic heart disease. One can perhaps speak of the fulminant, protracted, or comparatively benign forms of this disease and a similarity to tuberculosis may be envisaged. What accounts for this difference of clinical and pathologic course is unknown, but apparently it exists principally in the patient himself and is generally considered to be due to the poorly understood factor, resistance. In short, rheumatic disease is not a respecter of age; it prefers the company of youth, but may accompany the host to old age.

SUMMARY AND CONCLUSIONS

1. Disease of the mitral valve occurs with considerable frequency in patients in the older age groups. In consecutive autopsies on 177 patients who were 40 years of age or older at time of death, the mitral valve was found to be abnormal in eighty-one (46 per cent); in thirty-two (18 per cent) the etiology of the mitral valvulitis was considered to be rheumatic. Rheumatic disease was responsible for 40 per cent of the abnormal valves found in this series of patients.

2. The percentage of patients who showed abnormal mitral valves was almost constant (approximately 50 per cent) in each decade after the fourth:

The number in which rheumatic disease was the etiology showed a tendency to decline with advancing years. In our rheumatic series, women predominated.

3. The more extensive and deforming lesions of the mitral valve are likely to be of rheumatic rather than of degenerative origin. Mitral stenosis, including the atheromatous and calcific type, is, in the large majority, rheumatic in origin and is more likely to occur in women.

4. Evidence of a cellular inflammatory process was present in the mitral valve in 47 per cent of the patients in our rheumatic series. Among these there were seven in whom the process was considered to be acute; in two of these, Aschoff bodies were found in the myocardium.

5. Calcification frequently accompanies the rheumatic process and was seen on gross and microscopic examination in 47 per cent of the cases.

6. A positive clinical history was obtained in only a small proportion of the rheumatic cases (15.5 per cent). The clinical diagnosis of rheumatic heart disease is not usually made in older patients. Nine of our patients (28 per cent) showed no murmurs at the time of the clinical examination.

7. Rheumatic disease of the heart of various degrees occurs more often in the older age group than is clinically surmised. In many older patients the condition has a comparatively benign course.

The authors wish to acknowledge their appreciation to Dr. Douglas Symmers, General Director of Laboratories, City of New York, and to Dr. J. Murray Steele, Director of the Third (N. Y. U.), Medical Division, Goldwater Memorial Hospital, for their many suggestions with the preparation of this manuscript.

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Clinical Reports

CONGENITAL PAROXYSMAL TACHYCARDIA

REPORT OF CASE RECOGNIZED ANTE PARTUM

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THE total number of reported cases of paroxysmal tachycardia in infants, newly born or in their first year of life, is not large; there are probably many cases which go unrecognized. In 1941 Hubbard¹ was able to find only nineteen well-established cases in infants under 1 year of age. To these he added nine new cases, six of which he had observed during the course of a single year.

It is not known at what stage of intrauterine life paroxysmal tachycardia first develops. Two cases of paroxysmal tachycardia, recognized prior to birth, have been reported.^{2,3} In one the arrhythmia was first noted during the twenty-four hours immediately preceding birth and in the other, it was recognized a month prior to delivery. The case to be presented is that of an infant in whom tachycardia was recognized by the attending obstetrician* three months prior to birth at full term.

CASE REPORT

On Jan. 30, 1945, while examining a woman at the end of her sixth month of pregnancy, the obstetrician observed that the fetal heart rate was very rapid. Since the tachycardia, estimated to be 200 to 250 beats per minute, was also present on five subsequent examinations during the next three months, he concluded that the fetus had a paroxysmal tachycardia and so informed the mother one month prior to her delivery.

On April 29, 1945 (2:35 P.M.) he delivered, at St. Luke's Hospital, a full-term white female child weighing 8 pounds and 1½ ounces. Delivery was by forceps control and was uncomplicated. Aspiration with a Dann machine was carried out because of slight delay in respiration. On examination of the child the only abnormality noted was a heart rate of 228 per minute. On the following day the rate was 210 per minute.

An x-ray film of the chest on this day showed cardiac enlargement mainly to the left of the midline. The maximum transverse diameter of the heart measured 5.5 cm. as compared to 9.6 cm. for the maximum internal diameter of the thorax. There was no abnormality of the lungs.

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The first electrocardiogram was taken on May 1, 1945, forty-four hours after birth (Fig. 1, *A*). This showed a supraventricular tachycardia arising in the upper portion of the atrioventricular node at a rate of 200 per minute. It was decided to give the infant digitalis, and an electrocardiogram (Fig. 1, *B*) was taken the following day after the equivalent of 0.05 Gm. of digitalis in the form of digifolin had been given intramuscularly. The tachycardia was found to be replaced by sinus rhythm with a rate of 125 per minute. After every second ventricular complex, a blocked P wave was seen. These P waves were sharply inverted in Leads II and III and were of the same general outline as those recorded during the tachycardia. This indicated that the premature auricular contractions were arising at or near the same focus responsible for the tachycardia.

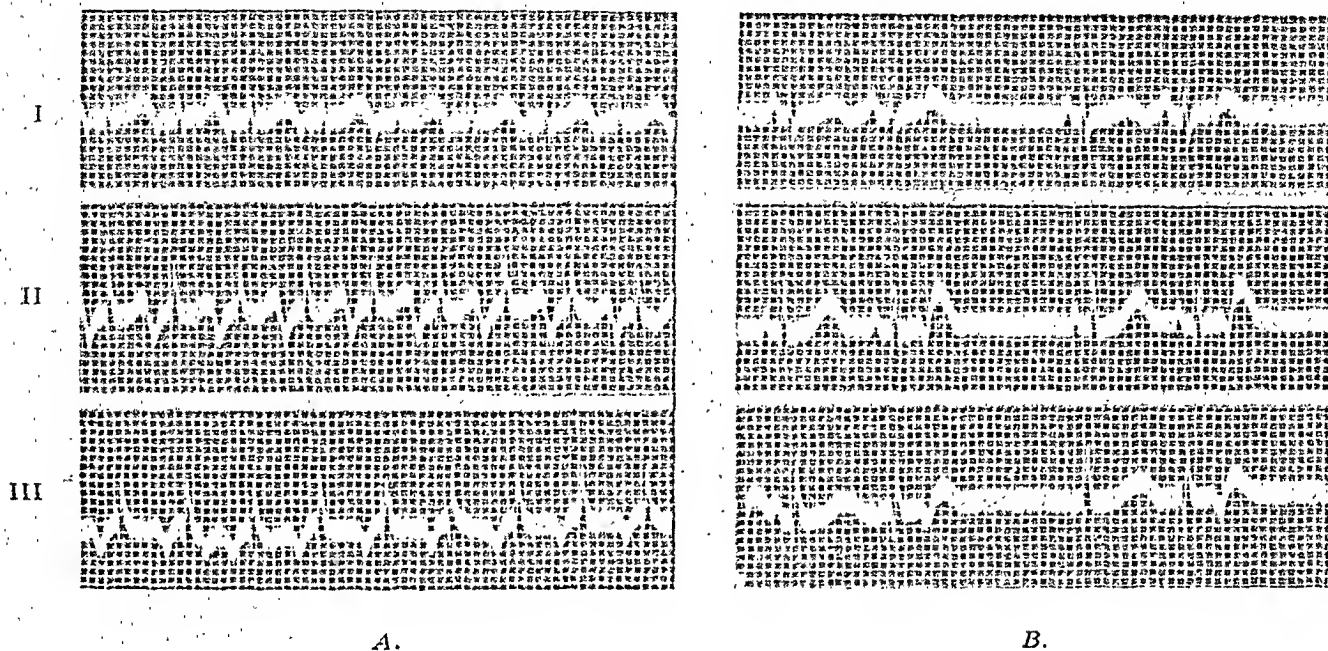


Fig. 1.—*A*, May 1, 1945, forty-four hours after birth. Supraventricular tachycardia arising in the upper portion of the atrioventricular node. The rate is 200 per minute.

B, May 2, 1945, twenty-four hours after intramuscular administration of the equivalent of 0.05 Gm. of digitalis in the form of digifolin intramuscularly. Sinus rhythm has been restored. Following every second ventricular complex there is a nodal extrasystole which is blocked.

Although digitalis had been effective in stopping the tachycardia, it was evident that the ectopic focus was still active. However, in order to give digitalis a sufficient trial, it was continued for two more days and the next electrocardiogram was made on May 4, 1945. In this record (Fig. 2) the tachycardia was present for the most part but was interrupted occasionally by short periods of normal sinus rhythm.

At this point digitalis was discontinued and the infant was given 10 mg. of quinidine sulfate four times daily on the first day, 20 mg. on the second, and finally 30 mg. four times daily on the third day. This dosage was effective and was considered reliable for stopping the tachycardia and restoring normal rhythm.

On May 9, the parents demanded the infant's release. Her condition was good and the parents were instructed to give quinidine, 30 mg., every six hours. They were taught how to detect the presence of tachycardia by applying the ear over the infant's precordial area. This they readily learned which made it possible to direct them to decrease the number of doses when the tachycardia was not present. After the infant was 2 months old, quinidine was given only on those infrequent days when excitement or prolonged crying precipitated a paroxysm.

On Aug. 14, 1945, when the child was nearly 4 months old, the electrocardiogram (Fig. 3) was normal in all respects and showed a conspicuous increase in the voltage of the QRS complexes in all leads.

The child continued to develop normally and at the time of the last examination on Oct. 26, 1945, she weighed 16 pounds and 10 ounces. No quinidine had been used and no abnormal cardiac rate had been noted since the child was $3\frac{1}{2}$ months of age.

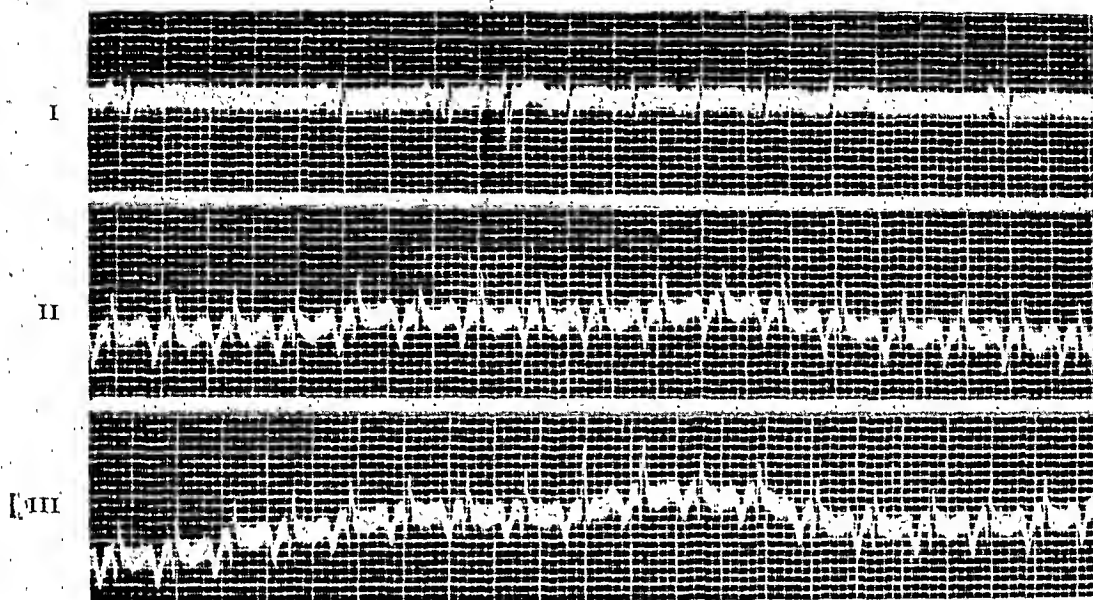


Fig. 2.—May 4, 1945, after the equivalent of 0.15 Gm. of digitals. The nodal tachycardia is present but intermittent. Superimposed upon the T wave of the first ventricular complex in Lead I there is a small negative deflection representing a premature auricular contraction which is blocked.

After the third ventricular complex a similar deflection is followed by a short period of tachycardia with aberration of the first QRS complex of the series.

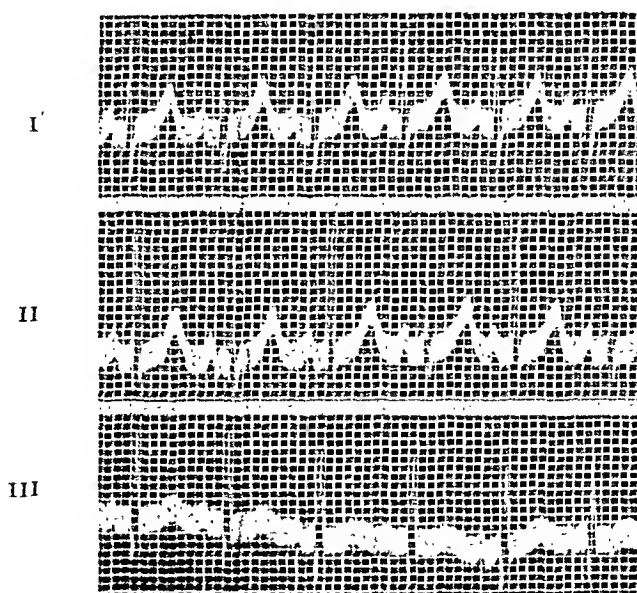


Fig. 3.—Aug. 14, 1945. Normal electrocardiogram.

SUMMARY

A case of congenital paroxysmal tachycardia recognized three months prior to the birth of the child at full term is reported. Single daily doses of the equivalent of 0.05 Gm. of digitalis given intramuscularly on three successive days failed to control the tachycardia. Quinidine sulfate in 30 mg. doses by mouth at six-hour intervals was more effective.

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DIFFUSE SCLERODERMA WITH INVOLVEMENT OF THE HEART

REPORT OF A CASE

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SCLERODERMA as it affects the skin has been well known for years but it is only recently that it has become generally recognized as a diffuse systemic disease of the collagenous tissue which may involve all organs containing connective tissue.¹ It, therefore, resembles diffuse lupus erythematosus which at first was recognized as a skin disease and later became known as a generalized systemic disease. In scleroderma, lesions have been described involving the gastrointestinal tract from the buccal mucous membrane to the colon.²⁻⁵ The definite and characteristic involvement of the heart and lungs has been well described by Weiss and co-workers,^{6,7} who first used the term "scleroderma heart disease." Lesions have been found in most visceral organs containing collagenous tissue.⁸⁻¹¹

The reason for reporting this case is that it demonstrates the clinical picture and characteristic pathologic changes of the myocardium, as first described by Weiss, and thus helps to confirm the existence of scleroderma heart disease as a specific clinical and pathologic entity.

REPORT OF CASE

First Admission.—A 23-year-old single woman, who did clerical work, was admitted to the Royal Victoria Hospital on March 10, 1944, complaining of gradually increasing stiffness and tightness of the skin with increasing sensitivity to cold for the past five years. For the last three years there had been a slowly developing brownish pigmentation of the skin and during the last year she had suffered from palpitation, weakness, and dyspnea on exertion.

She first noticed that the skin on the index finger of the left hand became white, then yellow, after which it became stiff and appeared "tight." In the beginning, the lesions subsided with the onset of menstruation and relapsed afterward. The nail of the index finger was lost. The skin became very susceptible to trauma and small, slowly healing ulcers would appear. The process of tightening of the skin extended to all the fingers of both hands, the arms, and the rest of the body and limited movement of the joints. The increasing stiffness of the face interfered with smiling and opening the mouth. Since the appearance of the first lesion, the patient had noted an increased sensitivity to cold which caused the fingers and toes to turn blue and feel numb. This also happened on emotional excitement. The skin pigmentation increased. Six months before admission the patient began to experience cardiac palpitation and weakness on

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exertion and vertigo, especially in the morning. Her appetite was poor and she had lost 16 pounds during the past year. Past and family histories were noncontributory.

Physical Examination.—The patient was a moderately well-nourished woman in no apparent distress. The skin over the entire body appeared thickened and fixed to the underlying tissue. It was tightly drawn over the bony prominence where there were scars of healed ulcers. Small ulcerations were present on the index finger of the left hand and over the lateral malleolus of the left ankle. The fingers and toes were cyanotic and cold, but this disappeared shortly after admission. The only other positive findings were a palpable left lobe of the thyroid, multiple extrasystoles, a blood pressure of 106/75, and a palpable liver and spleen. Special examinations showed a normal blood chemistry and a basal metabolic rate of -9 per cent. Roentgen examination of the hands revealed no changes in the bony texture. A biopsy taken of the skin showed an increase in the thick collagenous fibrils of the corium. The diagnosis was scleroderma and acrocyanosis. Treatment with mecholyl, 10 mg. four times a day, subcutaneously, was initiated for the relief of the acrocyanosis. After a two-week stay in the hospital the ulcers were healed and the patient was discharged.

Second Admission.—On March 13, 1945, the patient was re-admitted, complaining of increasing tightness and pigmentation of the skin. She was able to move her joints only with great difficulty. Sensitivity to cold was greatly increased. She had been forced to discontinue her work four months before admission because of severe weakness and fatigue. Ulcers, which appeared on the nose, the tip of the elbow, and the knuckles during the menstrual periods refused to heal as they had done in the past; instead they gradually increased in size. Palpitation and dyspnea on exertion were more severe. Four days before admission the patient began to have constant pain in the right upper quadrant of the abdomen associated with nausea and vomiting of normal gastric contents. Palpitation increased and she experienced continual mild precordial pain which was relieved by bed rest.

Physical Examination.—The brownish discoloration, marked stiffness, and tightness of the skin had increased. The fingers, arms, and legs were partly fixed in a semiflexed position with indolent ulcerations on the tip of the nose, the elbows, and the knuckles. The chest showed diminished excursions on both sides with harsh breath sounds and scattered coarse râles over both bases posteriorly. The blood pressure was 115/90. The heart was moderately enlarged to percussion, its rhythm was irregular due to frequent extrasystoles, its sounds were diminished in intensity, and a harsh systolic murmur was present at the apex. The liver was 2 cm. below the costal margin and slightly tender. The spleen was not palpable. There was slight pitting edema of the ankles.

Laboratory Findings.—The urine showed a specific gravity of 1.020, a faint trace of albumin, and occasional red and white blood cells. The blood studies and complete hemogram were within normal limits. The basal metabolic rate was -5 per cent. The blood Wassermann and blood Kahn were negative. Blood nonprotein nitrogen, cholesterol, proteins, albumin-globulin ratio, bilirubin, serum sodium, calcium, inorganic phosphorus, and carbon dioxide capacity were normal. An electrocardiogram (Fig. 1) showed an arrhythmia due to extrasystoles, left axis shift, A-V conduction time of 0.24 second, slurred and low-voltage QRS complexes, and diphasic T waves with depressed RS-T intervals in Lead I. The circulation time was 37 seconds and the venous pressure 220 mm. of water. Roentgen examination showed the heart to be definitely increased in size in all its diameters (Fig. 2). There was a dense shadow present at the base of both lungs. A barium meal showed a normal esophagus, stomach, and duodenum. Endocrine assay of the urine revealed a 17 ketosteroid output of only 2.7 mg. per liter in a twenty-four hour volume. (Normal for this laboratory is 12 to 15 mg. per liter.)

Progress and Therapy.—During her stay in the hospital the temperature remained normal. The dietary intake was adequate. Shortly after admission congestive failure increased and a diastolic gallop rhythm appeared. Digitalis was, therefore, given, with a fair response. Because of low ketosteroids the patient was given 10 mg. methyltestosterone three times a day with considerable improvement in the texture of the skin of the face and hands after two weeks' treatment. During the last week in the hospital she suffered from recurrence of substernal tightness and constriction, more evident when excited or emotionally disturbed. The signs of congestive failure

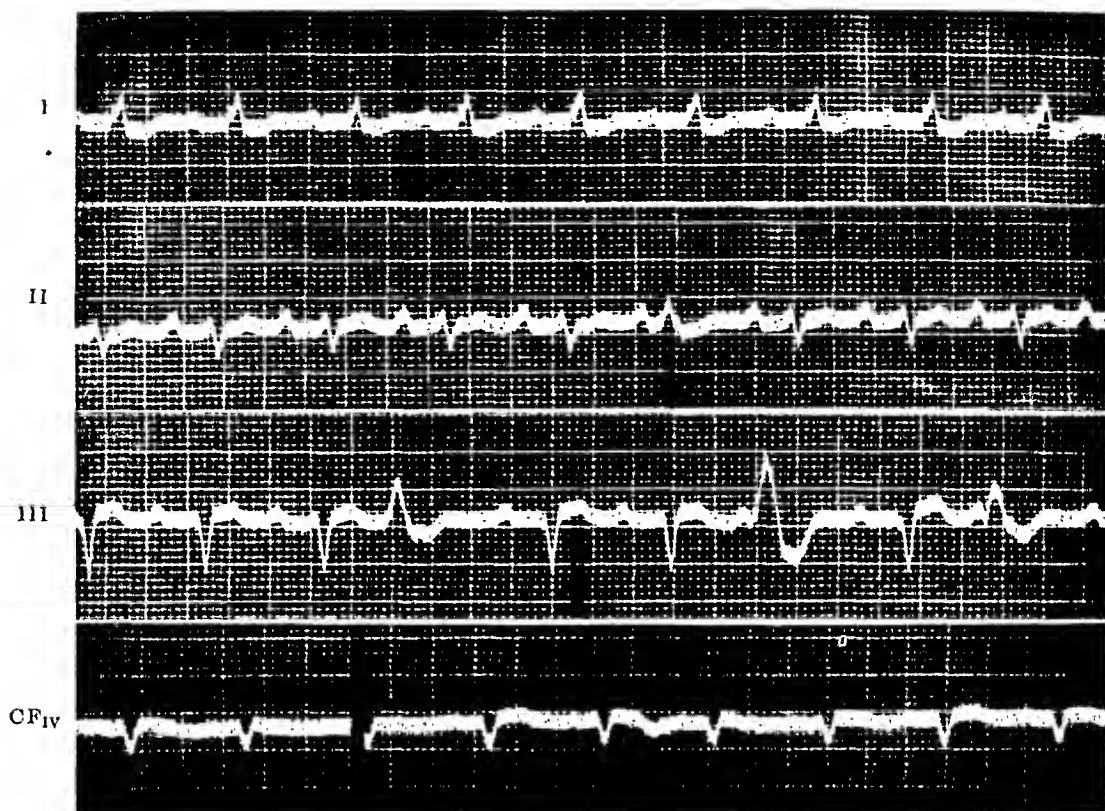


Fig. 1.—Electrocardiogram recorded one week before death, showing abnormalities noted in text.



Fig. 2.—X-ray film of the chest showing definite enlargement of the heart with dense shadows present at the base of both lungs.

recurred. Two days before her death she complained of pain in the left chest and the following day expectorated blood-tinged sputum. A friction rub was heard in the left axilla. Her condition deteriorated and she died six weeks after admission.

Post-Mortem Examination.—Necropsy was performed two and one-half hours after death. The following is a summary of the positive findings. The body was that of a well-developed and fairly well-nourished white woman. The skin showed diffuse brownish pigmentation and thickening. Pale patches were present over the right knee and above the pubis. The index fingers were ulcerated and all fingers were semiflexed; they had a clawlike appearance and were difficult to extend. Horny areas were present over both malleoli, over both elbows, and on both buttocks. The free margins of the left ear felt nodular and calcified. The hair was black in color and of the usual female distribution.

The pericardial cavity contained about 300 c.c. of amber-colored fluid. The epicardium showed a white spot on the anterior surface of the left ventricle about 3 cm. in diameter. The heart weighed 290 grams and there was some dilatation of both ventricles. There was a fresh mural thrombus on the endocardium at the apex of the left ventricle. The coronary arteries were patent throughout, and no evidence of obstruction was found down to their finest ramifications. Both pleural cavities were obliterated by dense pleural adhesions and the lungs were subcrepitant on palpation. The peritoneal cavity contained about 200 c.c. of amber-colored fluid. Nothing unusual was noted in the gastrointestinal tract. The liver showed passive congestion.

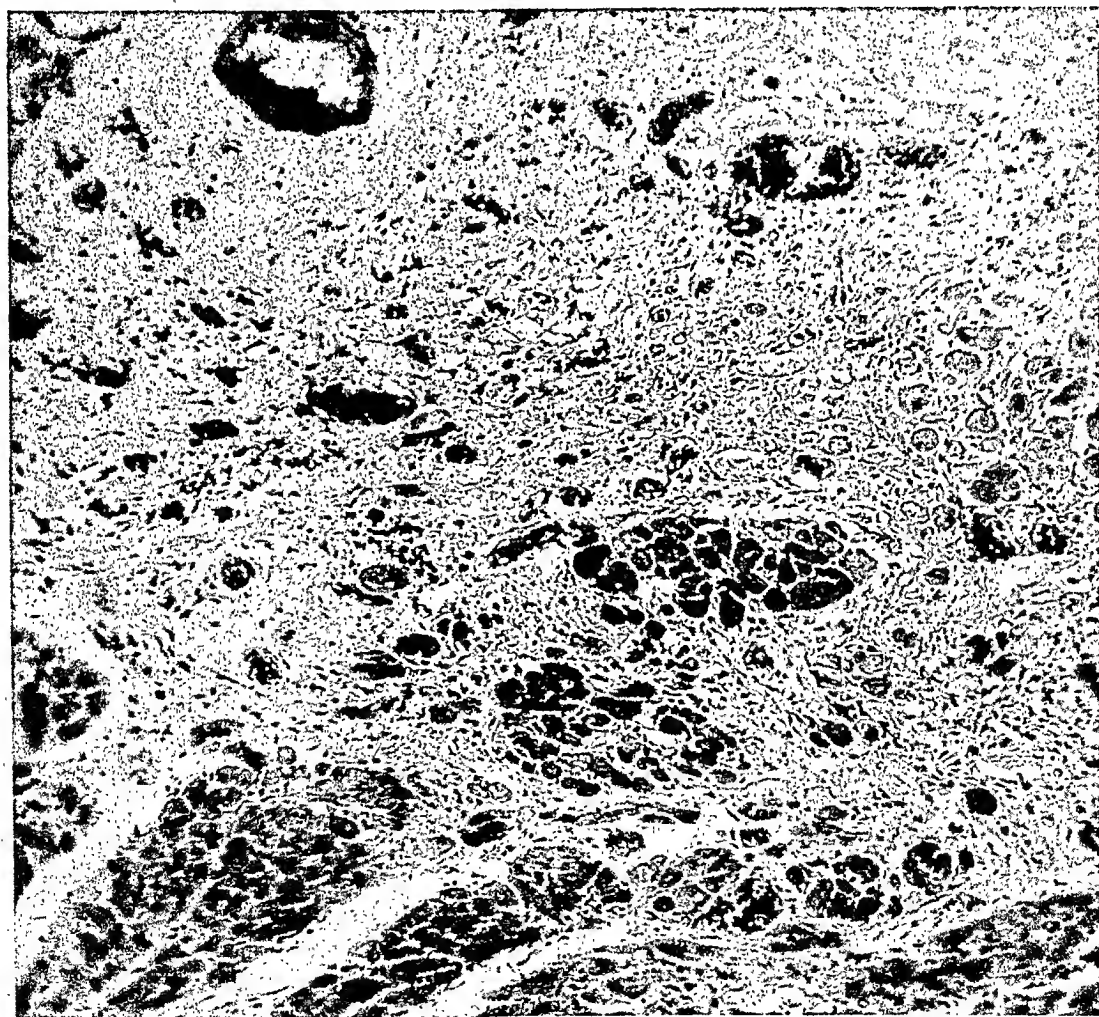


Fig. 3.—Photomicrograph of the myocardium showing a focal area of diffuse fibrosis. There are a few chronic inflammatory cells scattered throughout the fibrous area. Note the islands of intact myocardium surrounded by fibrosis. Some of the muscle fibers in these islands show evidence of varying degrees of degeneration. There are many patent arterioles seen in the section (X110).

The pancreas, adrenals, and spleen appeared normal on gross examination. The right kidney had two small fresh infarcts in the cortex and the left kidney had one. The brain and its coverings appeared normal.

Microscopic Examination.—Focal areas of fibrotic scarring were distributed diffusely throughout the myocardium and did not appear to bear any relation to the vascular tree. In some areas there was infiltration with lymphocytes and monocytes. In places the collagenous bundles were thickened, hyaline, and somewhat eosinophilic; such areas were present in parts of the heart valves. The endocardium and epicardium had areas of collagenous thickening. There was an organizing thrombus at the apex of the left ventricle. Some of the small arteries and arterioles presented thickening of their medial layers with some stenosis of their lumina (Fig. 3). The pleurae were

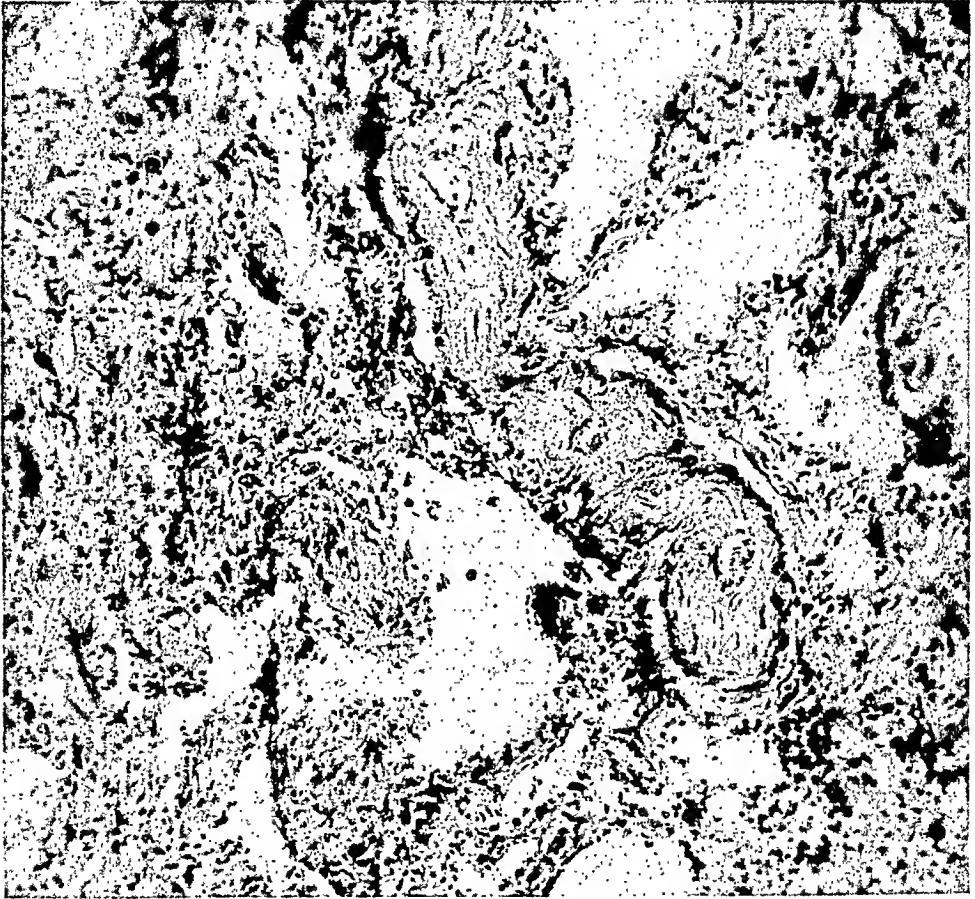


Fig. 4.—Photomicrograph of a section of a lower lobe of the lung showing diffuse fibrotic thickening of the alveolar walls with obliteration of some of the alveolar spaces. Note the adventitial thickening of the arteriole in the center of the section ($\times 110$).

thickened by collagenous tissue. In places they showed fibrinoid necrosis as demonstrated by a smudgy red appearance in the hematoxylin and eosin stain and by a red color with Masson's trichrome stain. The lower lobes of the lungs presented a diffuse interstitial fibrosis with obliteration of many alveolar spaces (Fig. 4). The kidneys showed infarction and some "wire loop" lesions of the glomeruli, but the latter were present only to a slight degree. The psoas muscle had irregular patches of hyaline fibrosis. The liver showed evidence of passive hyperemia and fatty infiltration.

In the skin, the epidermis was thinned and the rete pegs were flattened. The melanin content of the basal layer of the epidermis was diffusely increased. Some granules of melanin pigment were seen in the superficial portion of the corium. The superficial dermis showed a fusion

of its components into a smooth hyaline mass. The collagenous tissue in the deeper areas of the dermis was thickened and hyaline but the individual fibers were more distinct than in the superficial layers (Fig. 5). Masson's trichrome stain showed some areas of red staining denoting fibrinoid degeneration of the collagenous tissue.

The lymph nodes had a generalized lymphoid hyperplasia, the capsules and stroma being thickened by collagenous tissue. The larger arteries throughout the body did not show any specific changes. The remainder of the tissues showed no abnormalities.

Anatomic Diagnoses.—These included diffuse scleroderma with acrocyanosis and sclerodactylia, ulceration of the skin of both index fingers, fibrosis of the myocardium, endocardium, and epicardium, dilatation of the heart, mural thrombus of the heart, hydropericardium, embolism of renal arteries, infarcts of kidneys, interstitial fibrosis of lungs, chronic passive hyperemia of liver, ascites, fatty liver, calcification of the left auricular cartilage, and pigmentation of the skin.



Fig. 5.—Photomicrograph of a section of the skin from the abdomen showing increase in cornification and thinning of the epidermis with flattening of the rete pegs. The collagenous fibers in the superficial corium are diffusely swollen and increased in number. Note the discrete area of lymphocytic infiltration in the corium near a hair follicle (X110).

COMMENT

The early history of this case is typical of scleroderma as it affects the skin. The definite remissions noted with the onset of menstruation and exacerbations afterward, the low ketosteroids, and the favorable response of the skin changes to methyltestosterone seem to favor the theory that an important etiologic factor

in scleroderma is an endocrine dyscrasia. There was no evidence of other toxic factors, such as ergot poisoning,¹² or disturbance of the parathyroid¹³ or of the thyroid gland⁸ which have in the past been incriminated as causing scleroderma. Raynaud's syndrome appeared after the early skin changes had been established and this can hardly have been the initial cause of the disease as suggested by Brodie.¹⁴

The symptoms of cardiac involvement appeared about two years before death and after the skin changes were well advanced, but the actual cause of death was congestive heart failure. The associated pulmonary lesions and the interference with thoracic movement by the tight skin of the thoracic wall no doubt contributed to the failure of the already damaged myocardium. There is no clinical or pathologic evidence of any other condition which could account for the myocardial lesions. There was no past history of the common infectious diseases in childhood such as scarlet fever and diphtheria. Rheumatic fever is eliminated both by the clinical and the pathologic findings. In the gross examination of the heart no lesions of the valves were found. There were no typical Aschoff bodies present and the fibrotic areas in this case were not concentrated around the mitral valve ring or in the subendocardial tissues of the left atria.

Acute and subacute endocarditis are discarded as etiologic factors because of the clinical picture and the absence of vegetations on the heart valves. The myocardial lesions showed no evidence of acute inflammatory exudate. Pyemia is also eliminated by the absence of a primary site or of metastatic lesions and by the negative post-mortem heart blood culture and the appearance of the fibrotic lesions. The blood Wassermann and blood Kahn reactions were always negative and there was no evidence of aortitis. The lesions did not resemble those ascribed to syphilis; in fact the existence of syphilitic myocarditis is questioned by many pathologists.¹⁵

The coronary arteries were patent down to and including their smallest ramifications. Hypertension is eliminated both by the clinical picture and the absence of definite hypertrophy of the heart. Helminthic, protozoal, and viral agents were not found. There was no history of administration of any of the sulfonamides, so that the lesions in the myocardium could not be ascribed to sulfonamide sensitivity.¹⁶ Serum sickness, uremia, poisoning with various chemicals, burns, all of which have been known to cause variable lesions in the myocardium, are manifestly not concerned in the present case. No pathologic lesions suggestive of tuberculosis were found. Disseminated lupus erythematosus may involve the heart muscle but the typical skin lesions and other systemic features were not present. The lesions in the heart did not resemble those ascribed to this condition. Diffuse isolated myocarditis must be discarded as a diagnosis in this case because of the presence of the typical skin lesions of scleroderma. Diffuse myocarditis on the basis of a vitamin deficiency^{17,18} is not likely because of the past history of an adequate diet. It seems logical to conclude, therefore, that the damage to the cardiovascular system and lungs was part of the diffuse scleroderma.

The pathologic findings in the skin in this case are characteristic of those described in the textbooks.¹⁹ They can best be interpreted as dependent on a change in collagenous connective tissue. The existing collagenous fibers in the corium become thickened and new ones are formed. In the earlier stages this collagenous tissue is infiltrated in some areas with moderate numbers of lymphocytes and monocytes. The inflammatory cells diminish in quantity as the lesions develop and the collagenous tissue changes become predominant. The collagenous tissue in some areas appears to have undergone fibrinoid degeneration as shown by Masson's trichrome staining method.

The fibrosis of the lungs found in this case has been described by others.⁷ Whether it is specific for scleroderma is open to question. Similar lesions are found in cases of organizing pneumonia and in chronic passive congestion. They do, however, resemble the picture of generalized scleroderma and could be explained by an increase of the collagenous tissue in the lung parenchyma. The kidney lesions were not so marked as those described by others.¹⁰ The gastrointestinal tract was free from the lesions lately described by Bevans.⁵

The lesions in the heart are almost identical with those described by Weiss and co-workers⁷ and gave rise to definite clinical signs and symptoms. Here again the primary lesion appears to be an overgrowth of collagenous fibers in focal areas throughout the myocardium which extend to the endocardium and pericardium in some areas. These fibrotic areas encroach upon and damage or completely destroy the adjacent myocardial fibers. The fibrosis does not appear to be on the basis of impaired myocardial circulation because, as already mentioned, many patent arterioles were found scattered throughout these areas, and no obstruction was found in the coronary circulatory system.

Clinically and pathologically, it appears that all changes in function and structure observed in this case must be attributed to the diffuse disturbance of collagenous connective tissue which is characteristic of scleroderma.

SUMMARY

1. A case of diffuse scleroderma with characteristic and specific involvement of the heart has been described.
2. Other conditions causing myocardial lesions have been excluded.
3. The specific pathologic changes in the collagenous tissues have been described.
4. Relation to menses, low ketosteroid output, and favorable response to methyltestosterone suggest endocrine disturbance as a possible etiologic factor in this case.

The authors gratefully acknowledge the helpful advice and criticism of Dr. J. C. Meakins and Dr. G. Lyman Duff.

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MULTIPLE LIVER ABSCESES WITH RUPTURE INTO THE PERICARDIUM

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THE infrequency of sudden rupture of a liver abscess into the pericardial cavity is apparent from the few cases reported in the literature. Huard and Meyer-May⁴ observed this complication three times in 150 cases of liver abscess. Ochsner and DeBakey⁷ found one example in 181 liver abscesses (amebic). Vergoz and Hermanjot-Gerin,¹⁰ however, found this condition in thirteen of eighty patients with amebic liver abscess. This complication is most likely to occur, for obvious reasons, in those patients not operated on. The mortality rate for liver abscesses with their complications is reported by Ochsner, DeBakey, and Murray⁸ to be 79.6 per cent (432 cases). This was in a series of collected cases, whereas in a series of 102 patients not operated upon, the mortality was 100 per cent; on the other hand, in a series of 151 cases in which operation was performed, Ochsner, DeBakey, and Murray⁸ report a mortality of 50.9 per cent. It is interesting that the origin of multiple liver abscesses is in the appendix in only about 13 per cent of all patients^{6,9}; the abscesses are cryptogenic in about 59 per cent of the patients.⁸

CASE REPORT

An 18-year-old soldier, American-born but of Italian descent, was admitted to a regional hospital Nov. 10, 1945, and died Jan. 10, 1946. His illness began during the first week of September, 1945, while at another camp. His chief complaint was "pain in the stomach." The story was one of rather sudden epigastric pain, sharp in character, and constant though not excruciating. He awakened with the pain on the morning of September 7 and it continued all day. He had eaten a little food but noticed no exaggeration of the pain afterward. He had been on sick call four times in the first three weeks and had been given some liquid medicine and sent back to duty. The bowels had been regular. There was no nausea or vomiting. He stated that he "had fever" off and on during this period. The pains persisted and he continued to stress the upper abdomen rather than the lower abdomen. The localization, as far as one could tell, was in the epigastrium. There was no headache, upper respiratory infection, constipation, or diarrhea accompanying the onset; nor were there any chills recorded then or later, except following two of the blood transfusions (Type O, weak Rh positive).

First Hospitalization.—On admission Sept. 29, 1945, the temperature was 101°F.; the pulse rate, 76; and the respirations, 20 per minute. The patient was noted to have a flaky macular eruption on the shoulders, upper arms, and back; this rash had not been noticed until admission and disappeared after a few days. In addition, there was tenderness bilaterally in the costovertebral angles. During the course of illness he developed an enlarged liver which extended from

two to four fingerbreadths below the right costal margin. These were the only physical findings at the time. Despite chemotherapy consisting of sulfathiazole, sulfadiazine, and 2,000,000 units of penicillin, the temperature continued to reach 103 to 104° Fahrenheit.

In the initial count, the white blood cells were 22,950 with 75 per cent neutrophils and 8 per cent stabs. The urine showed albumin 2 plus, pus, red blood cells, and a few granular casts. The nonprotein nitrogen of the blood was 58.3 mg. per cent. During his stay in the hospital he ran a persistent leucocytosis. Anemia (2,950,000 red cells; hemoglobin, 9.6 Gm.) developed rapidly. Several cultures of catheterized urine specimens were negative, but on September 30 a culture showed hemolytic *Staphylococcus aureus* and *Staphylococcus albus*, coagulase negative.² Many stool cultures were negative except during one brief period of diarrhea which lasted one day (October 16) and was not related apparently to the epigastric pain, when a *Shigella*, Boyd 88 was cultured. Numerous blood cultures were negative. Liver function tests revealed the following: the cephalin flocculation test was 4 plus and there was an increased prothrombin time (patient, 22 seconds; control, 15 seconds, 68 per cent of normal). Total proteins were 7.5 per cent; albumin, 2 per cent; globulin, 5.5 per cent. The albumin-globulin ratio was 0.36 on October 13. One month after admission, the nonprotein nitrogen was 38 mg. per 100 c.c.; all agglutinations, including the Weil-Felix, as well as the complement fixation for murine typhus, were negative. An intravenous pyelogram showed normal contour and normal mobility of both kidneys. X-ray films of the chest were negative. The only abnormality on a film of the abdomen (October 22) was an enlarged liver.

Second Hospitalization.—On Nov. 10, 1945, the patient was transferred to a regional hospital at Fort Jackson for further treatment. He was admitted with a diagnosis of fever of undetermined origin. His only complaint was epigastric pain. He appeared extremely ill. His complexion was pale and sallow. His face was drawn and anxious, and the eyes were dull. His appetite was poor and constipation was present.

The patient was 5 feet, 2 inches tall and weighed 97 pounds (normal weight, 130 pounds). The temperature was 100.6°F.; the pulse, 100; and the respirations, 24 per minute. He was of small stature, the skin was warm and moist, and his nutrition was poor. The sclerae were clear; neither icterus nor petechiae were present.

One examiner thought there was limitation of movement of the right dome of the diaphragm, but otherwise the chest examination was considered to be negative. Fist percussion in the right lateral and posterior areas of the lower chest did not elicit any unusual response.

The heart size was within normal limits; the sounds were normal; no murmurs were heard. The heart rate was 100 per minute. Blood pressure was 100/85.

The liver was enlarged one fingerbreadth below the costal margin and was slightly tender to pressure. Most of the tenderness was in the epigastrium slightly to the left of the midline, no mass was felt here. Rectal and prostatic examinations were normal.

There was no edema and the deep reflexes were normal. The peripheral vessels were palpable and normal. Pulsations were present in the dorsalis pedis and posterior tibial vessels.

There were 19,900 white blood cells with 72 per cent neutrophils, 8 per cent stabs, 19 per cent lymphocytes, and 1 per cent eosinophiles. The red blood cells numbered 3,480,000 and the hemoglobin was 11 grams. Repeated urinalyses showed albumin 1 plus to 4 plus, red blood cells, white blood cells, and granular and hyaline casts. Blood cultures during November were still negative. On November 10 the prothrombin time was 80 per cent of normal. The nonprotein nitrogen was now 27 mg. per cent. A brucellergen skin test was negative. All agglutinations were negative. The total proteins were 8.1 per cent: albumin, 3 per cent; globulin, 5.1 per cent. The cephalin flocculation test was 4 plus. The sedimentation rate was 32 mm. in one hour (Wintrobe). A Fishberg³ concentration test shortly after admission showed a specific gravity of 1.011 (this later improved under therapy to 1.022). A test for urobilinogen was positive in a dilution of 1:20 but negative in a dilution of 1:40. The Van den Bergh test, both direct and indirect, was negative; the icterus index was 8. The Kahn test was negative. Stool examinations were persistently negative for pathogens. On December 4 a flat plate of the abdomen was negative.

Fluoroscopically, the diaphragm was normal in position and appeared to move freely. On December 14 fluroscopic and radiographic examination of the lungs and heart were negative. Electrocardiogram made on November 23 was normal (Fig. 1).

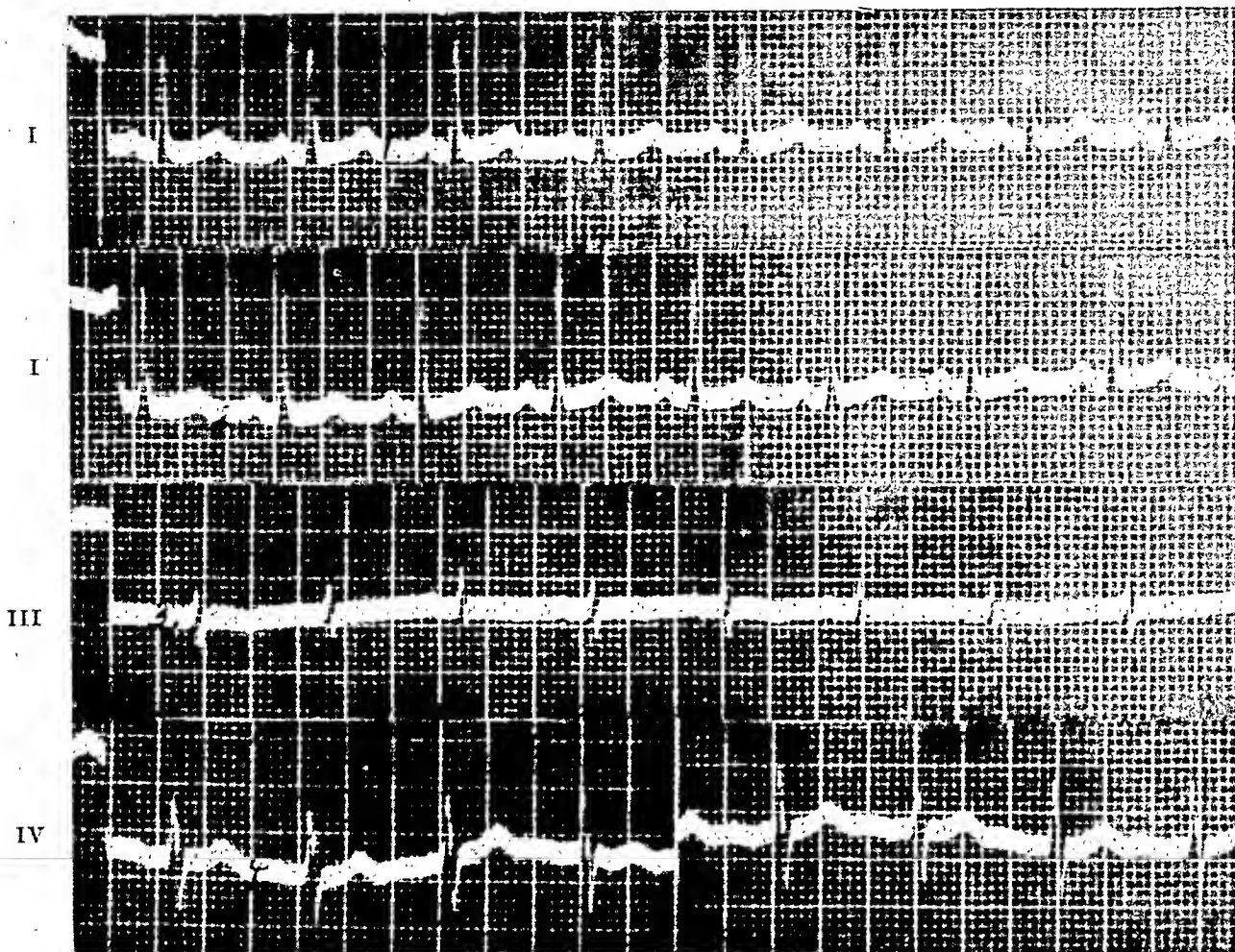


Fig. 1.—Nov. 23, 1945. Rate, 100; normal record.

Because of his poor physical condition, the patient was given repeated blood transfusions for a period of eight weeks. During this period he also received 19,050,000 units of penicillin at three-hour intervals, the dose being 30,000 units at first and 80,000 units later. This produced no effect on the temperature curve, except during the last week of penicillin therapy, when the maximum temperature was 99.6° Fahrenheit. In all other ways, however, he appeared much better: he was more alert and contented, his appetite improved, and there was a gain of four pounds in weight over a four-week period. The erythrocyte count reached a high of 4,250,000, although the leucocytes continued to average 19,000 with 82 per cent polymorpho nuclear cells. By Jan. 2, 1946, he felt so well that he requested discontinuance of the penicillin; with some reluctance this request was complied with inasmuch as the continuous injections over a period of eight weeks, day and night, were a hardship. He was cheerful and began walking about the ward. On January 4, at noon, he left the ward without permission and participated in a lively ball game on the lawn nearby. On January 6, shortly after noon, while playing cards, he suddenly developed severe substernal pain which radiated to the back and to the anterior part of the neck. An x-ray film of the chest made shortly after onset of this pain was negative (Fig. 5). The pain was severe, steady, and aggravated by breathing and movement of any type. He was in profound shock. There was no nausea or vomiting at first, but vomiting occurred thirty-six hours later. The patient was given morphine and penicillin, 80,000 units every three hours, and placed in an oxygen

tent. He continued to have thoracic pain and discomfort, although this was not as excruciating as at the onset. On January 7 physical examination disclosed an increase in the cardiac dullness to the left as far as the anterior axillary line. On January 8 posteroanterior and right and left anterior oblique films of the chest showed a mild diffuse enlargement of the heart shadow in which the normal contours of the heart were preserved (Fig. 6). There appeared to be small collections of fluid in both costophrenic sulci, slightly greater on the left side. There was also a small amount of vascular engorgement of the pulmonary tree and of the great vessels. Roentgenographic evidence suggested that fluid was present in the pericardial cavity. The white count was now

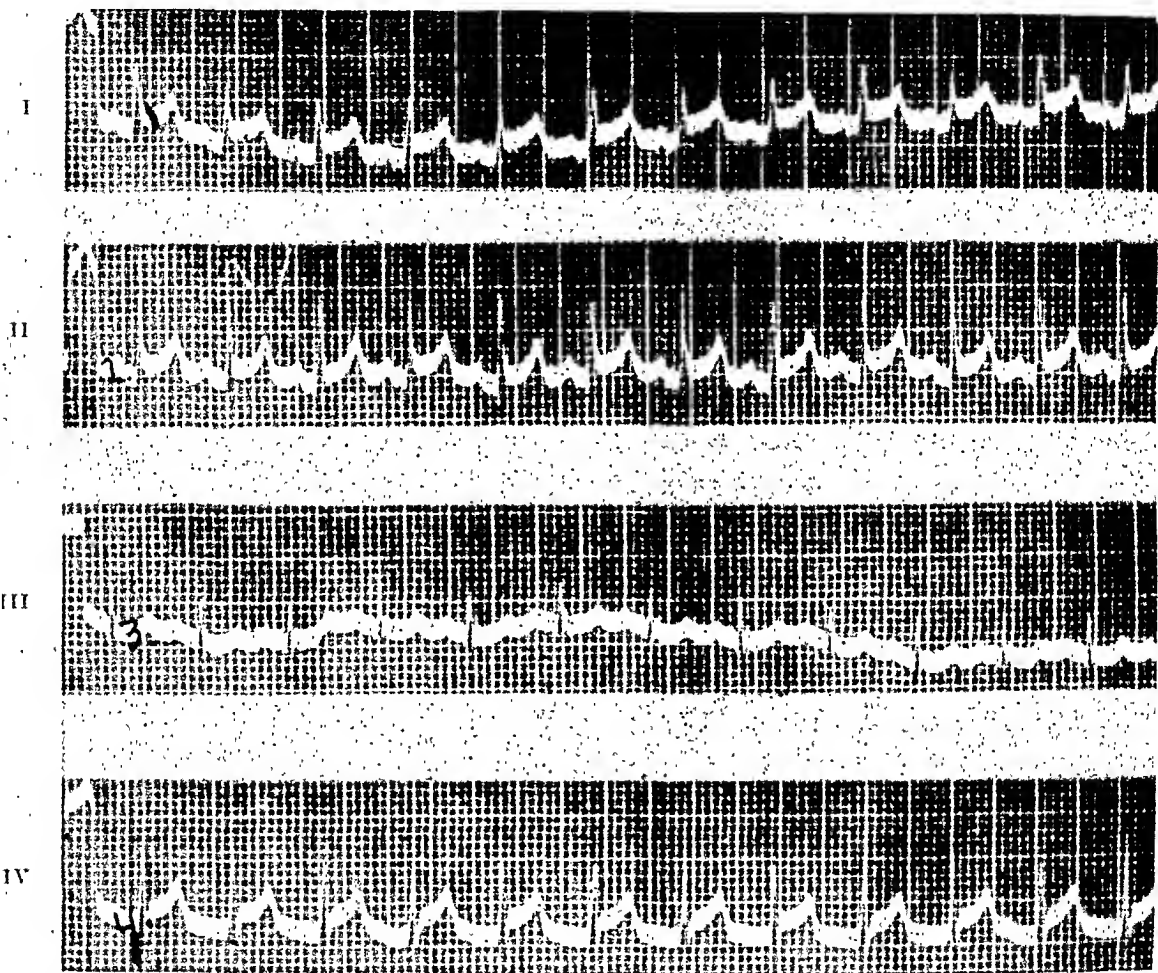


Fig. 2.—Jan. 7, 1946. Twenty hours after rupture. Tachycardia 150; elevated RS-T segments Leads I and II. Findings characteristic of acute pericarditis.

40,000 with 90 per cent polymorphonuclear cells. Posteriorly there were percussion changes and suppression of the breath sounds at the left lung base. A coarse friction rub, synchronous with respirations, was heard in the fifth interspace in the anterior axillary line. The heart rate was accelerated. The sounds were of poor quality and distant. No murmurs were heard. Blood pressure was not obtainable. The radial and brachial arteries could not be felt; pulses paradoxus was not elicited in the carotid arteries. The electrocardiogram now showed changes characteristic of acute pericarditis (Figs. 2, 3, and 4). There was coldness and cyanosis of upper and lower extremities. No pericardial rub was present. The pleural rub had disappeared. The patient ran a progressively downhill course and expired suddenly while his pillow was being changed on Jan. 10, 1946, two days after onset of acute chest episode.

Clinical Diagnosis.—(1) Multiple pyogenic liver abscesses with rupture into the pericardium and left pleural space. (2) Possible hemopericardium, associated with necrotizing arteritis (polyarteritis).

Necropsy Findings.—When the peritoneal cavity was opened, 1,500 c.c. of clear amber-colored fluid was recovered. The peritoneal surfaces were smooth and glistening; the loops of intestines were normally disposed. The omentum hung, apronlike, over the intestinal loop in the upper half of the peritoneal cavity. The loops of the small bowel were distended with gas and

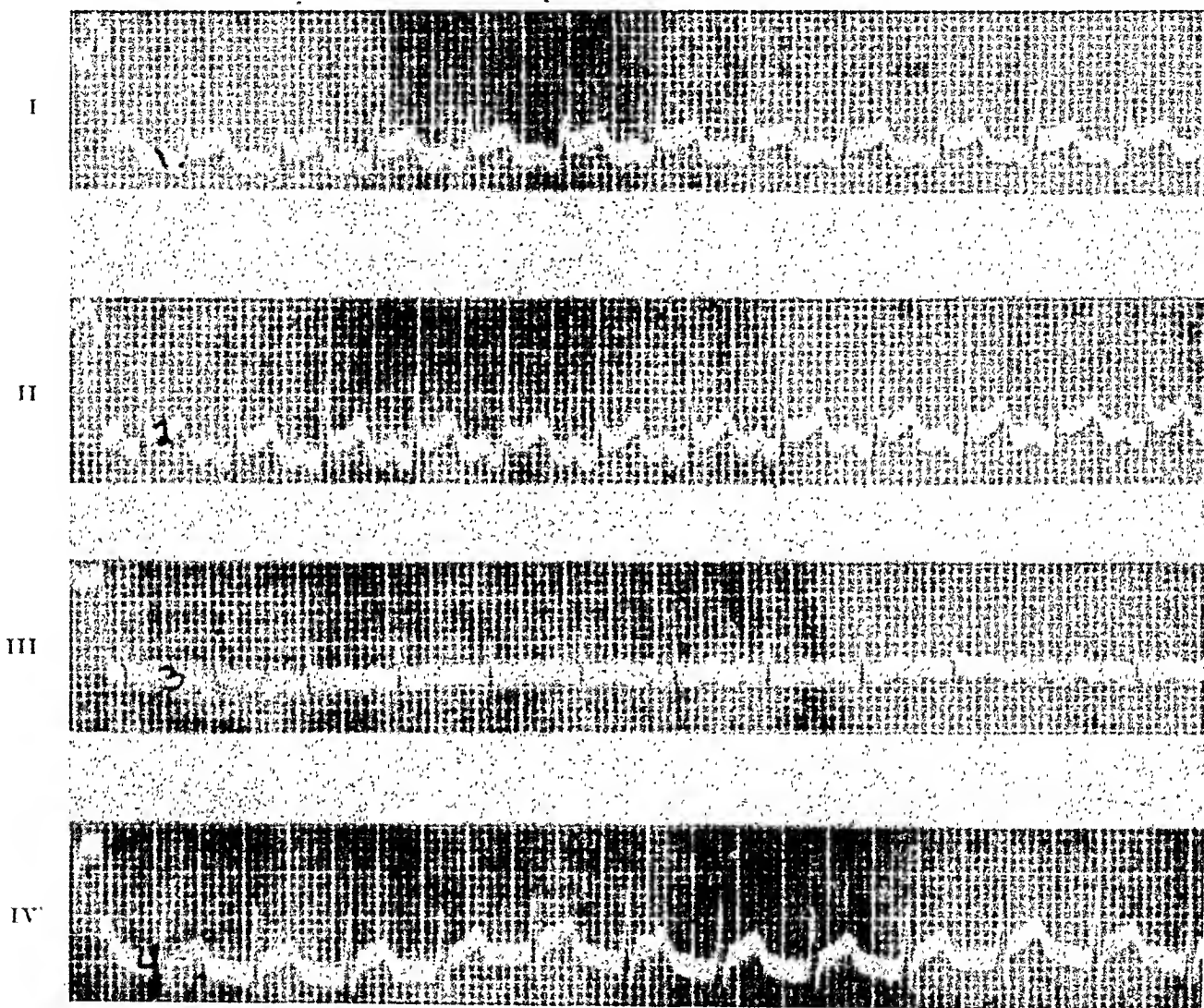


Fig. 3.—Jan. 8, 1946. Forty-eight hours after rupture. Low voltage QRS₁ and QRS₃, elevated RS-T segments in Leads I and II. Findings typical of acute pericarditis.

were hyperemic. Palpation and section of the portal vein radicals revealed nothing other than nonclotted dark red blood. The appendix was present and normal in appearance. The lower edge of the liver extended 5 cm. below the costal cage in the midclavicular line on the right. The diaphragm was adherent to the upper surface of the liver on both sides. The fibrous adhesions were delicate and friable on the right but were dense on the left. The diaphragm extended to the level of the fifth rib on the right and the fourth rib on the left. On opening the pleural cavity, the right lung was found to be partly collapsed and about 300 c.c. of turbid, straw-colored fluid were present. The left lung was collapsed to a similar degree and an estimated 150 c.c. of the same type of fluid were present in the left pleural space.

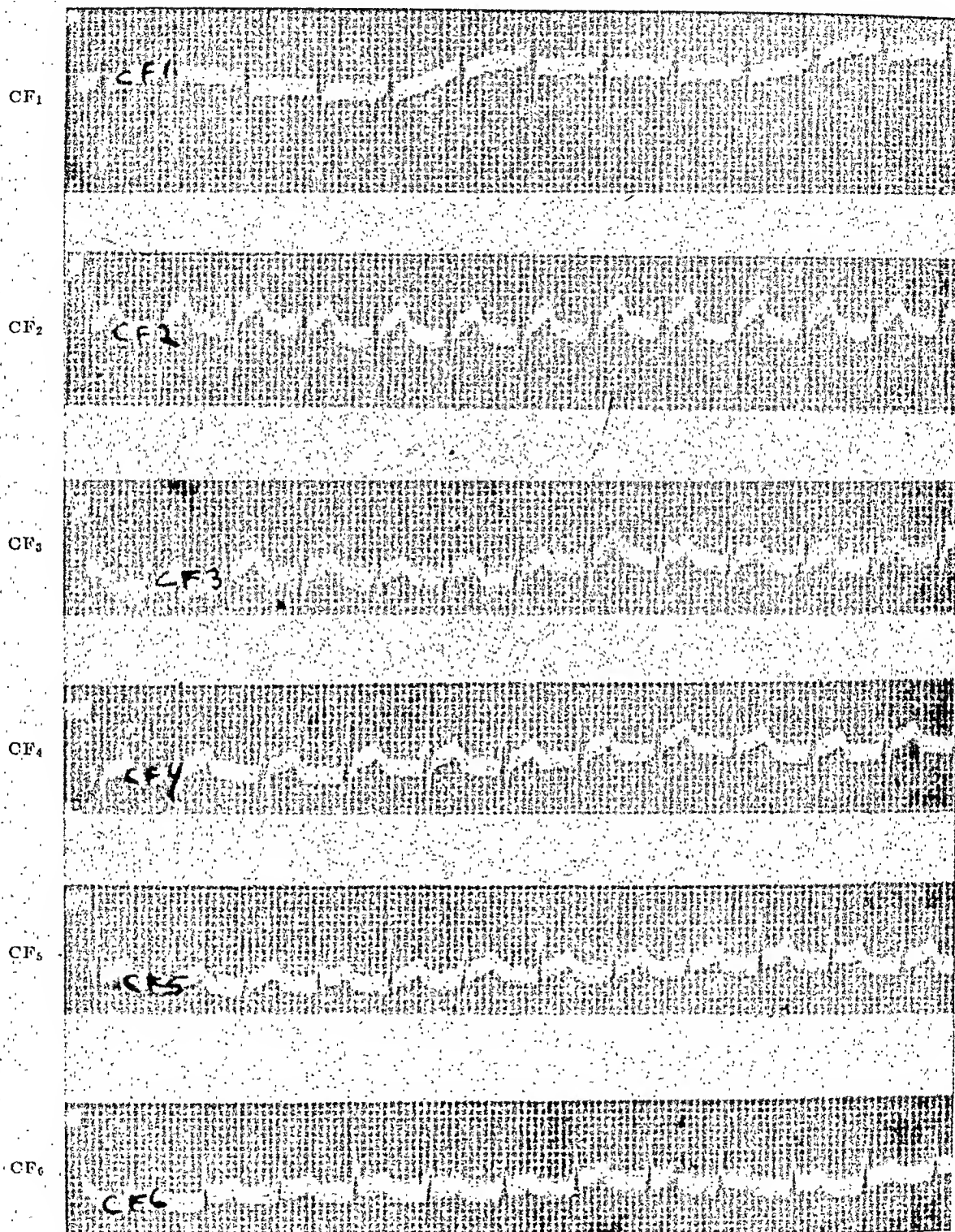


Fig. 4.—Jan. 8, 1946. Chest leads (CF series) taken at same time as limb leads shown in Fig. 3. Essentially normal except for slight depression of S-T segment and flattened T in CF₁.

The pericardial sac was very greatly enlarged and was thickened and fibrous. The walls were tense and translucent. Delicate, fibrous adhesions existed between it and the contiguous pleural surfaces. This sac extended from the level of the sternoclavicular joint to a point in the left chest which was 9 cm. from the midline in the fifth intercostal space. The upper portion of the pericardial sac was 5 cm. in width in the sternoclavicular area and extended 6 cm. to the right of the midline at the level of the second interspace. The pericardium when opened was found to contain 400 c.c. of greenish-yellow turbid fluid. Floating in this fluid were large, ragged, light yellowish-green clumps of fibrinopurulent exudate. The parietal and visceral pericardium were

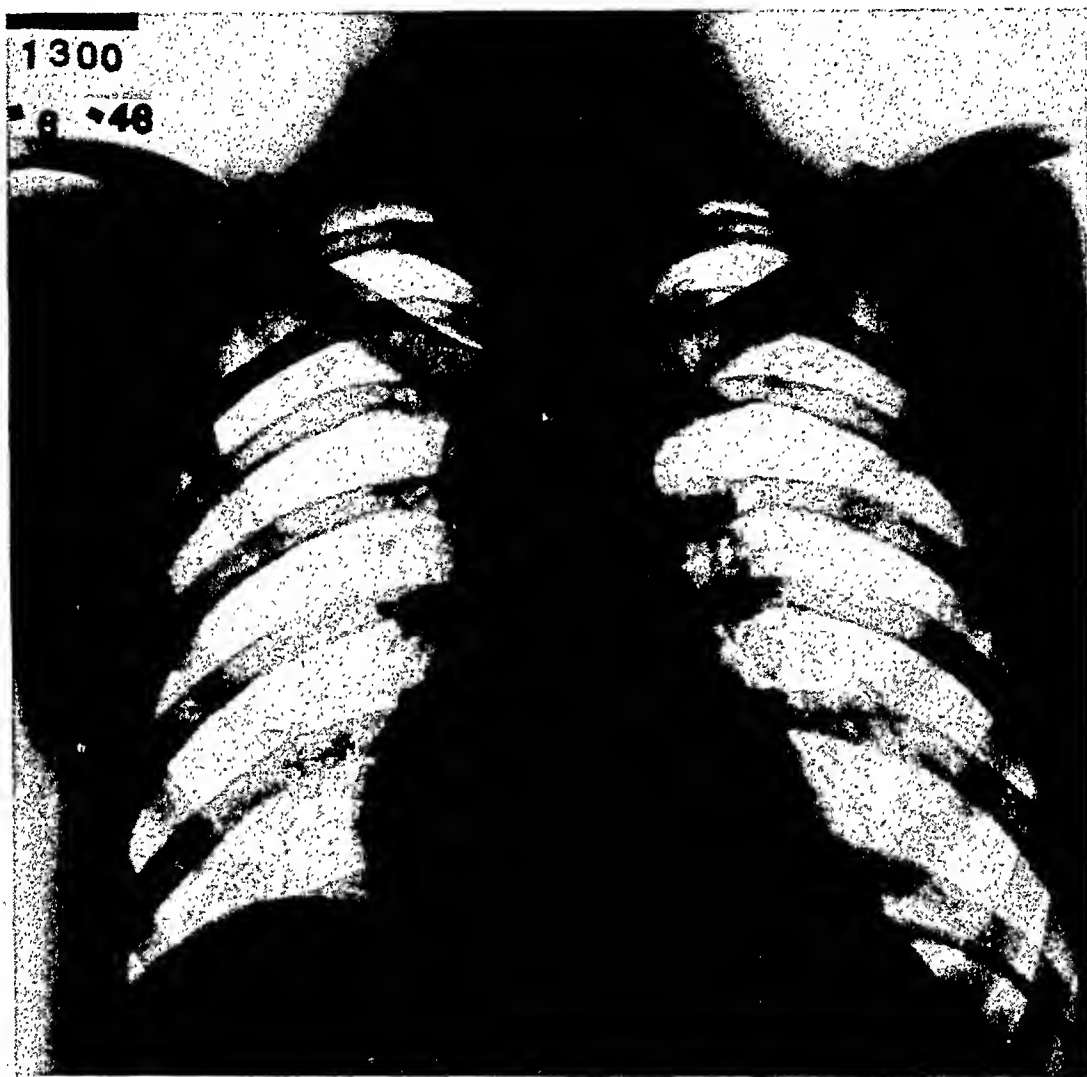


Fig. 5.—On day of rupture, x-ray negative. Size and contour of heart unchanged from previous films.

covered with a shaggy but delicate fibrinous exudate. This exudate covered all surfaces of the heart and great vessels so thickly that underlying epicardium was obscured. No gross perforations were demonstrated in the pericardium. The heart weighed 360 grams. The left ventricular myocardium was 9 mm. thick and that of the right ventricle was 4 mm. thick. The endocardial surfaces were normal as were the valve leaflets. The internal surface of the ascending aorta was light yellow in color and smooth in character. The coronary ostia were of the usual size. The left lung weighed 380 grams and the right 390. The lower lobes of both lungs were dark red. On section the cut surfaces revealed congested dark red lung tissue from which frothy sanguinous fluid exuded on pressure.

The liver weighed 1,980 grams. When the dense fibrous adhesions connecting the uppermost portion of the left lobe and the diaphragm were dissected, there was found a large left subphrenic abscess which involved 65 per cent of the left diaphragmatic area. This abscess cavity contained 175 c.c. of thick, light jade-green pus. Further dissection revealed a tract which led from the subphrenic abscess to a necrotic abscessed area involving the left lobe of the liver. Around this tract the diaphragm was so densely adherent to the surface of the left lobe that dissection could only be accomplished with sharp scissors. The upper surface of the left lobe showed a moderately deep concave deformity caused by the adjacent subphrenic abscess. On



Fig. 6.—Forty-eight hours after rupture. Diffuse enlargement of heart shadow in which normal contours are preserved. Small collection of fluid in left costophrenic sulcus. Widening at base not entirely due to pericardial fluid but to vascular engorgement of pulmonary tree and great vessels.

section, the right lobe presented a nutmeg appearance. Sections further to the left revealed that the upper one-half of the left lobe and a small portion of the adjacent middle lobe contained light yellow-brown necrotic hepatic tissue in which there was cavitation in the area of the tract that communicated with the left subphrenic abscess. In all these cavities the same type of light green, thick, purulent material was present. The gall bladder showed no abnormalities. The gastrointestinal tract showed no gross pathologic change in its entire course. Each kidney weighed 220 grams. There were small subcapsular hemorrhages present over the upper poles of both kidneys. On section the normal renal architecture was present. The cortex and medulla were hyperemic. The adrenals were normal as were the ureters, urinary bladder, prostate, and testicles.

There were no striking changes in the spleen. The pancreas was normal. The brain showed some gross hyperemia and edema of the cortex. No abnormalities of the vascular or neural patterns were observed.

The smear and culture of the abscess fluid revealed *Staph. aureus*, nonhemolytic.

Anatomic Diagnosis.—(1) Acute fibrinopurulent pericarditis. (2) Chronic subphrenic abscess. (3) Chronic passive hyperemia of the lungs. (4) Chronic focal suppurative hepatitis, with multiple abscesses of left lobe of liver.

DISCUSSION

In this particular case it was felt that the liver abscesses were multiple and the patient too poor a risk for surgery. Some may argue, with statistical justification,⁸ that surgery should have been attempted. After viewing the autopsy, however, it was felt that drainage would have been inadequate because the numerous abscesses in the left lobe were inaccessible to any surgical approach. On the other hand, Huard and Meyer-May⁴ reported a case of solitary abscess of the left lobe of the liver followed by an aseptic puriform pericarditis with recovery after trans-sternoxiphoid drainage; the abscess was located with iodized oil. It was also of interest that about two weeks prior to the sudden rupture of the abscess, we attempted to detect limitation of motion of the diaphragm by fluoroscopy but were unable to see anything but normal movements. The location of the pathology in the left lobe of the liver undoubtedly accounts for this.

The rupture of the abscess into the pericardium followed by four days the cessation of penicillin therapy and by two days the violent exercise on the lawn. The acute episode, when it occurred, looked like an acute vascular accident; coronary thrombosis, hemo-pericardium, or rupture of a dissecting aneurysm was thought possible. One excellent observer, who had not previously seen the patient, thought of a polyarteritis with necrotic changes in the vessel walls which might have been responsible for the bizarre general symptomatology as well as for a possible sudden pericardial hemorrhage. The electrocardiogram had shown changes characteristic of an acute pericarditis and the latter suggestion seemed reasonable. The possibility of liver abscess rupturing into the pericardium, however, was thought more likely. A pericardial tap was suggested for diagnostic purposes but since evidence of effective tamponade was not present, conservatism prevailed and it was not done.

The electrocardiogram taken twenty hours after onset (Fig. 2) showed typical changes of acute pericarditis mainly in the first two limb leads. Forty-eight hours after onset, the limb leads were unchanged (Fig. 3). The six chest leads (CF series) added little; the only definite finding was an extremely low voltage T wave in CF₁, with slight S-T depression⁵ (Fig. 4). The remaining chest leads were within normal limits. The electrocardiograms are of interest in that the changes which they revealed were not seen in any of the very few case reports of this complication of liver abscess.^{1,4}

SUMMARY

1. A case of multiple pyogenic liver abscess with complicating sudden rupture into the pericardial sac is presented.
2. The source of the liver abscess was not found at necropsy.
3. Penicillin, 19,050,000 units, plus supportive therapy over an eight-week period, held the infection in abeyance but did not overcome it. The responsible organism was penicillin sensitive as judged by the clinical response.
4. Typical electrocardiographic changes of acute pericarditis were demonstrated in the limb leads, with minimal findings in the chest leads (CF series).

The author wishes to acknowledge the suggestions and comments on this case by the following: Lieutenant Colonel Walter C. Bartlett, Major Griffith Radcliffe, and Major Jacob Silverman, Medical Corps, Army of the United States. The necropsy was performed by Captain Edwin Albright.

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In Memoriam

CARL J. ROTHBERGER

1871-1945

Friends of Professor C. J. Rothberger of Vienna will learn with deep regret that he was killed during the war when his home was hit by an aerial bomb.

With his demise, medicine has lost one of the last great investigators of the classic period of electrocardiography. His identification of the total irregularity of the pulse, the delirium cordis, with auricular fibrillation (in collaboration with Winterberg) met with resistance and was accepted only when Sir Thomas Lewis made the same discovery independently soon afterward. Rothberger described bundle branch block in the experimental animal (with Eppinger) and also in man. A series of fundamental studies on the influence of the tonus of the cardiac nerves on the electrocardiogram, on auriculoventricular rhythm, and on the origin of extrasystoles followed. In collaboration with Kaufmann, parasystole was described and analyzed in a series of papers. The hope that extrasystoles with fixed coupling could be based on a parasystolic mechanism was not fulfilled, but a new and interesting disturbance was discovered. In the later years, the studies on the mechanism of origin of extrasystoles were continued and the importance of the after-potential for the appearance of extrasystoles was investigated (with Goldenberg).

Rothberger had an unusual experimental skill which he improved early in his career in the laboratory of Pavlov. Afflicted with otosclerosis which caused almost complete deafness, he spent his days exclusively in the study of electrocardiographic problems. He had a clear and lucid style, and his reviews, particularly that in Volume 32 of *Ergebnisse der Physiologie*, are milestones in the science of cardiology.

In the years before 1938, physicians from all over the world, among them many from the United States, worked in his laboratory. He was to all an unselfish helper and advisor and with his kindly personality made a host of friends who will be saddened by the news of his death.

With the conquest of Austria in 1938 he lost his position, his library, and the opportunity to work or to publish the results of his studies. Unfortunately, he was not spared to live to see the day of liberation.

DAVID SCHERF
PAUL D. WHITE

CESARE PEZZI

1874-1945

Less than a year ago Europe lost one of its best cardiologists, a great soul, and a modest man. We can say "Europe" because Pezzi, though Italian, was known better in his adopted country, France, than in Italy.

A few years after he obtained his medical degree from the University of Pisa in 1899, Pezzi went to Paris and devoted himself to experimental research, first, in the Laboratory of Richet and later in that of Pachon. Then, attracted by the rising star of Vaquez, he joined him at the Hôpital de la Pitié and became one of his better known pupils.

Although his residence in Paris was meant to be short, it lasted about twenty years. These years were employed in continuous and fruitful work which included graphic studies on the apex beat and jugular pulse tracings, studies on premature beats, sinus arrhythmia, heart sounds, the action of calcium on the vagus nerve, production of auricular fibrillation, action of nicotine, A-V heart block, pulsus alternans, and gallop rhythm. Pezzi also studied congenital heart diseases and gallop rhythm. The vigorous pulsation of the pulmonary vessels, described by him in pulmonic insufficiency, was later called hilar dance or Pezzi's sign. During the first years of this period he was one of the founders of the *Archives des Maladies du Cœur* in which many of his articles were subsequently published.

From 1915 to 1919 Pezzi took part in World War I, fighting with the Italian Army. Some studies on cardiac wounds were accomplished during his war service. At the end of the war he was one of the founders of the Italian periodical *Malattie del Cuore e dei Vasi* whose title was later changed to *Cuore e Circolazione*.

During the period 1919 to 1921, Pezzi worked again in France. Then, having lost his beloved wife, he went back to Italy and, on the advice of his friends, settled in Milan, near his home town. However, although Pezzi lived in Italy after 1921, frequent trips to Paris kept him in contact with the French school, as is proved by his books. One of them, *Roentgenology of the Heart and Vessels* appeared in Milan, but two others were published in France, in collaboration with Laubry. They are: *The Gallop Rhythms* and *The Congenital Diseases of the Heart*.

After his return to Italy, Pezzi tried in vain to obtain official recognition of his work. While recognized as a well-known specialist, he was unable to obtain any important position in the hospitals or in the medical schools. There were several reasons for this: his modesty, his long sojourn in France, and his uncompromising attitude toward Fascism.

The increasing fury of Fascism finally led to political persecution, so that Pezzi was obliged to lead a secluded life during World War II. For some time his friend Laubry was able to correspond with him at rare intervals; then news ceased completely.

The name of Pezzi should be preserved in the minds of all cardiologists, not only because of his work, but also because of his integrity and honesty which have been recognized by friends and enemies alike.

A. LUISADA

Abstracts and Reviews

Selected Abstracts

Ramos, J. G., and Peralta, B.: Action of Digitalis and Ouabain on Certain Properties of the Myocardium. Arch. Inst. cardiol. Mexico 16:93, 1946.

The effects of various concentrations of digitoxin and ouabain on certain cardiac functions were studied by simultaneous electrical and mechanical recording. The heart rate, amplitude of isotonic contraction with different loads and different initial tensions, velocity of transmission of the impulse, and capacity to perform work were studied in isolated and perfused amphibian hearts. The velocity of transmission of the impulse and blood pressure changes were studied in cats under dial anesthesia.

These experiments revealed no consistent or clear-cut difference in the action of the two drugs. The authors suggest that the pharmacodynamic and clinical difference between them is due to one or more of the following factors: (a) different action on the autonomic nervous system, (b) different action on blood vessels, (c) different route of administration, (d) different degree of fixation by the tissues, (e) different rate of destruction or excretion.

Effective concentrations of both drugs shortened the P-R interval and increased the capacity for work but caused no change in the heart rate. Toxic concentrations of both drugs, on the other hand, slowed the heart rate and prolonged both the P-R and Q-S intervals, in addition to producing other well-known changes.

The authors attribute the increased capacity for work produced by these drugs to three factors: improved synchronization of the fibers during contraction, prolongation of the contraction, and decrease in the viscosity of the muscles. Toxic concentration of the drugs was found to increase the viscosity of the cardiac muscles.

LUISADA.

De Vries, A.: Changes in Hemoglobin and Total Plasma Protein After Injection of Mercurophylline. Arch. Int. Med. 78:181 (Aug.), 1946.

Various studies of the mercurial diuretics have indicated that their site of action is the kidney and that they produce diuresis by diminishing tubular reabsorption. Evidence that diuresis is the result of an extrarenal action is less convincing. The author considers that a primary extrarenal action of these drugs, which brings about a transfer of tissue fluids to the blood stream, would result in a temporary hydremia; that is, an increase in the plasma volume with a fall in hemoglobin and plasma protein. A preponderantly or exclusively renal action, on the other hand, would cause hemoconcentration. Fluctuations of hemoglobin and total plasma protein were therefore studied in 34 patients during the diuresis following injection of mercurophylline.

In patients who had edema, the average change in hemoglobin and in total plasma protein observed seven to twenty-eight hours after the injection of mercurophylline did not differ significantly from zero in statistical analysis. In patients in whom there was no edema, there was a significant rise in hemoglobin and in total plasma protein seven to twenty-eight hours after injection. In this group, the rise in hemoglobin and total plasma protein was higher with an increasing rate of diuresis. In the patients with edema, the changes in hemoglobin and total plasma protein were not dependent on the rate of diuresis.

These results indicate that a diuresis produced by mercuraphylline causes hemoconcentration which, in the presence of peripheral edema, is compensated by a rapid inflow of interstitial fluid into the blood stream. This interpretation is consistent with the theory of the renal action of mercurial diuretics.

BELLET.

Manchester, R. C.: Rheumatic Fever in Naval Enlisted Personnel: II. Effectiveness of Intensive Salicylate Therapy in Cases of Acute Infection. Arch. Int. Med. 78:170 (Aug.), 1946.

Studies of salicylate therapy were made in a series of seventy-seven young men with acute rheumatic fever, all of whom exhibited acute polyarticular arthritis as a major manifestation. Fifty-four patients received intensive salicylate therapy patterned after the regimen outlined by Coburn. Of this group, thirty-five received intravenously 10 Gm. of sodium salicylate in 1 liter of lactate Ringer's solution or isotonic sodium chloride solution daily for four to ten days; this was followed by oral therapy. The remaining nineteen patients received only oral therapy throughout the course of treatment. The twenty-three patients who comprised the control group received small quantities of salicylate for symptomatic relief of acute symptoms.

The results obtained in the intensively treated and the control groups were compared on the basis of temperature, articular manifestations, erythrocyte sedimentation rate, electrocardiographic and clinical findings, and the incidence of relapse and residuae. In the fifty-four patients who received intensive therapy, the average duration of fever was 36 days, and of objective articular manifestations, 2.8 days. In striking contrast, the average duration of fever in the control group was fifteen days and of objective articular manifestations, twenty-six days. The average duration of elevated erythrocyte sedimentation rate was twenty days in the intensively treated patients and forty-two days in the control group. The cardiac manifestations at the termination of treatment were carefully studied. Of the patients who received intensive therapy, 71 per cent showed no evidence of residual cardiac damage; 15 per cent were classified as having potential rheumatic heart disease on the basis of a slight or moderate mitral systolic murmur. Seven and four-tenths per cent of the intensively treated group had significant carditis when treatment was instituted. This process cleared up completely in all but one patient who was left with a moderate mitral systolic murmur. Significant cardiac residuae were present in 7.4 per cent of the group receiving intensive therapy; only one patient died of heart disease. Significant carditis did not develop in any patient who had not shown evidence of carditis before treatment was begun. In the control group, on the other hand, only 48 per cent of the patients escaped with undamaged hearts, 39 per cent were classified as having potential rheumatic heart disease, and 4.3 per cent had significant carditis which cleared up. In 13 per cent, significant cardiac residuae were present. The incidence of chronic infection, as determined by residual arthritis and increased sedimentation rate, was 6 per cent in the intensively treated group and 18 per cent in the control group.

The author concludes that the period of active infection is materially shortened and that relapses and residual chronic infection, although not prevented, occur less frequently in patients receiving intensive salicylate therapy than in those who receive symptomatic therapy. Except in occasional severe and refractory infections, salicylate administered orally is as effective as salicylate administered intravenously. Carditis present prior to treatment was favorably influenced by intensive salicylate therapy; resulting cardiac manifestations were distinctly less in the intensively treated as compared with the control group.

BELLET.

Bridges, W. C., Johnson, A. L., Smithwick, R. H., and White, P. D.: Electrocardiography in Hypertension: Study of Patients Subjected to Lumbodorsal Sympathectomy. J. A. M. A. 131:1476 (Aug. 31), 1946.

The authors describe the changes in the electrocardiogram which are frequently encountered in patients with diastolic hypertension after the reduction of blood pressure by lumbodorsal sympathectomy. A comparison was made between the preoperative and postoperative electrocardiograms taken two weeks and one year or longer after sympathectomy in the cases of 144 patients who were observed for at least one year. Preoperatively, these cases were divided into

three groups on the basis of pulse pressure in relation to the diastolic level. Type I comprised patients with the narrowest and Type III those with the widest pulse pressures. The following electrocardiographic changes were noted:

In the limb leads, 44.5 per cent of the preoperative records were abnormal or borderline. There was a progressive improvement in the abnormal records following operation. Sixty-seven per cent of the total series were normal two weeks postoperatively, and 78.5 per cent were normal at the end of a year. The most favorable group for operation, Type I, had the highest percentage of normal preoperative records. The greatest return to normal occurred in the most unfavorable group, Type III. Following operation, a swing of the electrical axis of more than 10 degrees toward the right took place in 34.1 per cent of the cases by the end of a year. R_1 decreased in amplitude more than 3 mm. in 41.7 per cent of the cases after one year. The T waves preoperatively were abnormal in 25 per cent of the cases. A year after operation the T waves were practically normal in Lead I in 86.1 per cent of the cases and in Lead II in 90.9 per cent.

In the chest leads, 50 per cent were abnormal preoperatively. There was a return to normal by the end of one year in 15 per cent. The T waves of the chest leads when abnormal, tended to improve in each lead postoperatively.

From this study, the authors conclude that when hypertensive patients with electrocardiographic evidence of cardiac strain, which is often the first manifestation of impending or actual heart disease, are subjected to bilateral lumbodorsal sympathectomy, they frequently show an improvement in the hypertensive electrocardiographic pattern one year or more postoperatively. This is consistent with the decreased work of the left ventricle.

BELLET.

Perrin, P.: Consideration of the Pathogenesis and Treatment of Functional Cardiac Symptoms in 50 Year Old Men. Arch. J. mal. du coeur 39:96 (March-April), 1946.

Symptoms of dyspnoea and tachycardia on effort, often accompanied by chest pain, are frequent in men about 50 years of age who have no objective evidence of heart disease. This type of illness is often very refractory to treatment. The author reports, however, that he obtained striking symptomatic improvement by the injection of vitamin B, 1 mg. every second day, and of testosterone, 25 mg. twice a week. The selection of medication was based on the views of Jayet-Lavergne that vitamin B has a specific effect on cellular polarization in the male. It is emphasized that although the explanation of the mode of action of the treatment is admittedly speculative, the clinical results have been most encouraging in a large group of patients who had received little or no benefit from other forms of therapy.

LAPLACE.

Leblanc, M.: Micro-Nodulation, a Manifestation of Pulmonary Stasis in the Presence of Mitral Disease. Arch. J. mal. du coeur 39:69 (March-April), 1946.

A case of mitral stenosis is reported in which x-ray examination revealed dense mottling throughout both lung fields due to the presence of miliary nodules and what appeared to be small cavities. This condition is easily confused with tuberculosis. Actually it is a rare manifestation of pulmonary stasis due to mitral disease. It is persistent and is not altered by clinical improvement in heart function. It has been ascribed to accumulation of carbon or hemoglobin due to stasis and intra-alveolar edema.

LAPLACE.

Lian, C., and Guinard, P.: The Practical Importance of Auscultation in the First Right Intercostal Space. Arch. J. mal. du coeur 39:92 (March-April), 1946.

The authors believe that the importance of auscultation in the first right intercostal space should be better appreciated. Systolic murmurs which arise from the aorta are almost invariably loudest in this area. There are two circumstances in which this fact may be helpful in diagnosis. When a patient is suspected of having mitral insufficiency and the systolic murmur extends to the base of the heart, if the murmur is best heard in the first right interspace, it is aortic in origin, irrespective of the presence or absence of mitral disease. When a systolic murmur is of equal intensity in the second right and left interspaces, it is aortic and not pulmonic if it is loudest in the first right interspace. Occasionally this area may also be the only site at which an aortic diastolic murmur can be heard.

LAPLACE.

Galli, F.: Considerations on a Rare Case of Dextrocardia (Isolated Dextrocardia With Inversion of the Chambers). *Cuore e circolaz.* 30:13 (No. 12), 1946.

The published cases of dextrocardia are reviewed and it is noted that when this congenital anomaly is isolated and not associated with inversion of other viscera, the cardiac chambers are usually in a position similar to that of a normal heart, but displaced to the right. A case is reported in which there was an isolated dextrocardia but the chambers were a mirror image of the normal. It is, therefore, the sixth published case of this rare anomaly.

The patient was an 18-year-old girl who complained of exertional dyspnea and palpitation. The heart was centrally placed, and there was an "apical" systolic murmur over the right side of the heart, transmitted to both the right axilla and the fourth left interspace. The spleen and liver were in normal position. A chest film revealed a "mirror-like" image of the heart, with the esophagus at the right of the spine but the stomach in the normal position. The general shape of the heart was rounded; the retrocardiac space was reduced. The right (actually the left) auricle was somewhat enlarged. The electrocardiogram showed a typical mirror-image appearance in Lead I; Lead II showed an inverted T wave.

The author attributes the electrocardiographic changes to inversion in the position of the conduction system in relation to the electrodes. The final diagnosis was dextrocardia with mitral valve defect.

LUISADA.

Kramer, Milton L., and Kahn, J. W.: The Effect of Atropine on the Branham Sign in Arteriovenous Fistula. *Arch. Int. Med.* 78:28 (July), 1946.

The phenomena of the Branham sign, which consists of the slowing of the pulse rate upon temporary obliteration of the arteriovenous fistula, suggests that it is due to a reflex arc in which the vagus nerve is the efferent pathway. Although patients with the larger fistulas show the most striking changes in pulse rate, the Branham phenomenon is also observed in patients with small fistulas.

The authors studied the effects of atropine on the elimination of the Branham phenomenon in patients with arteriovenous fistula. The heart rate, pupillary changes, and dryness of the mouth were utilized as evidence of atropinization. In nine of the ten cases thus studied, there was considerable fall in the pulse rate on obliteration of the fistula prior to atropinization, but the slowing failed to appear following administration of atropine. The changes in the blood pressure usually associated with obliteration of the fistula, namely, rise in diastolic pressure and reduction of pulse pressure, were not influenced by atropine.

BELET.

Chenoweth, M. B.: The Cardiovascular Actions of 2,3-dimercaptopopanol (BAL). *J. Pharmacol. & Exper. Therap.* 87:41 (Aug.), 1946.

BAL exerts its most important systemic actions on the central nervous and cardiovascular systems. Because of the presence of a pronounced circulatory effect, a detailed investigation of its action was made. BAL administered to cats intravenously resulted in a fall of the systemic and pulmonary arterial and venous pressures and in a rise of the portal pressure. When administered in very small repeated intravenous doses or by percutaneous application, BAL caused a rise in blood pressure. There was a marked rise in the peripheral resistance of the limb vessels during the period of falling blood pressure but none in the vessels of the liver or splanchnic areas.

Electrocardiograms (Lead II) were obtained in three anesthetized cats. Changes in heart rate were slight. Decrease in the voltage of the R wave, deepening of the S wave, elevation of the S-T segment, occasional ectopic beats, brief periods of ventricular tachycardia, and lowering of the T wave were observed at different times in the three cats.

Following the administration of BAL, the hematocrit reading was increased, while at the same time the concentration of injected dye in the blood was reduced. This paradoxical result is probably due to the loss of the dye from the blood stream. Blood volume, calculated on the basis of the hematocrit readings, was found to decrease by 30 per cent, whereas in the calculations

based upon the change in the dye concentration, the blood volume was found to increase by 27 per cent.

Administration of BAL resulted in a marked increase in the rate of lymph flow from the thoracic and cervical ducts.

The experimental data presented in this report supports the view that the major action of BAL on the cardiovascular system is twofold: a marked increase in capillary permeability as a result of the action of the drug on the walls of these structures; and a peripheral arteriolar constriction resulting from a direct action of BAL on the arteriolar structures. A third action, which is negative in character, is the absence of vasoconstriction of the splanchnic arterioles. The various changes in the circulatory system are probably secondary to these three phenomena. BAL presents a very interesting phenomenon from the pharmacodynamic point of view. The action of potent vasoconstricting agents is customarily regarded as being general throughout the vascular bed. The reaction to BAL is decidedly atypical in that peripheral arterioles are markedly constricted while splanchnic arterioles are unaffected. The action of BAL on the peripheral arterioles has been shown to be on the arteriolar structure, and it may be assumed that the sensitive component of the peripheral vessels is absent from the splanchnic bed. BELLET.

Ross, I. S.: Cerebral Vascular Occlusions in Young Adults. *J. Nerv. & Ment. Dis.* 104:51 (July), 1946.

The author reports a series of six cases of young adults who suddenly experienced a destructive cerebral lesion unaccompanied by subarachnoid bleeding and followed by permanent residual sequelae. These patients were free from syphilis, hypertension, atherosclerosis, bacterial endocarditis, and blood dyscrasias. In the absence of a final pathologic examination, no conclusion could be made as to the type of lesion which was present. The author believes, however, that the anatomical-pathological disorder common to these cases was a localized atherosclerosis such as has been found repeatedly in occlusion of coronary arteries in relatively young people. Death is unusual from a single cerebral infarction in this age group. BELLET.

Castro, V. Alzamora: The Influence of a Nonindifferent Electrode Upon the Precordial Electrocardiogram. *Gac. med. de Lima* 2:181 (Jan.), 1946.

The distorting influence of the potential variations of the extremities upon the precordial electrocardiogram in Leads C_L , C_F , and C_R is clearly demonstrated and the distortion is predicted by the use of unipolar limb leads. Although the alterations induced by the "indifferent" electrode when placed on one of the extremities are rarely excessive, the advantages of using a central terminal is emphasized on practical and theoretical grounds. HECHT.

De La Barreda, P., and Jimenez-Diaz, C.: The Action of Urinary Extracts of Normal and Hypertensive Individuals and of Hypertensive Dogs Upon the Arterial Pressure. *Rev. clin. españ.* 205:25 (Jan. 15), 1946.

Alcoholic extracts of urines from hypertensive patients and from dogs made hypertensive by cellophane perinephritis failed to cause an elevation of blood pressure in anaesthetized normal and hypertensive dogs and in rabbits. Some of the extracts showed hypotensive effects; others seemed to block and reverse the rise in pressure following epinephrine and alloxan. HECHT.

Cossio, P., and Sotomayor, O.: Paroxysmal Tachycardia With Syncope. *Prensa med. argent.* 33:903 (May 3), 1946.

Four cases are presented in which syncope occurred with the onset of attacks of paroxysmal tachycardia. In three patients the paroxysms arose from a ventricular focus and in one, from a supraventricular focus. The differential diagnosis of syncope in general is discussed and five types are listed: traumatic syncope (head or abdominal injuries), reflex syncope (carotid sinus syndrome), blood-loss syncope, orthostatic syncope, and cardiac syncope. The latter is further

subdivided into syncope following the onset of ventricular fibrillation, syncope occurring during a sudden onset of auriculoventricular block with failure of idioventricular rhythms to develop, syncope with cardiac tamponade, syncope "on effort" (Gallavardin), and syncope associated with paroxysmal tachycardia. The importance of an accurate diagnosis is again emphasized, for the treatment for one type may be contraindicated for others. Since syncope due to paroxysmal tachycardia is an infrequent event, the previous state of the heart muscle and the peripheral vascular system must be important contributory factors. The incidence of syncope is higher in ventricular tachycardias than in those of the supraventricular type because instances of the former are more commonly associated with cardiovascular disease.

HECHT.

Parra, J., and Franco, R.: Myocardial Changes Following Sulfonamides. Rev. clin. españ. 20:331 (Feb. 28), 1946.

A 69-year-old woman received approximately 50 Gm. of a sulfonamide over a period of ten days for an anthrax infection of the neck. Twelve days later pneumonia occurred and a second course of sulfonamide was prescribed, 7 Gm. daily for six days. The patient recovered but returned one month later with signs and symptoms of congestive heart failure. Treatment was unsuccessful and the patient died. At autopsy a few scars were found in the left ventricle, and a histological examination revealed what is merely described as "intense muscular degeneration and fatty infiltration." The absence of previous heart disease led the authors to assume that the myocardial changes were brought about by the excessive administration of sulfonamides.

HECHT.

Silbert, S.: Medical Management of Peripheral Vascular Disorders. Bull. New York Acad. Med. 22:397 (Aug.), 1946.

The author reviews the present-day treatment of arterial embolism, thrombophlebitis, arteriosclerotic disease of the extremities, and thromboangiitis obliterans and discusses briefly some important considerations in regard to treatment of these four conditions. In regard to embolism, he stresses the importance of elevating the head of the bed, the application of cold instead of heat, the use of vasodilator methods such as intravenous papaverine, one grain every two hours for four doses, and the use of continuous sacral anesthesia. In thrombophlebitis prophylactic measures such as daily exercises are stressed. An instance of severe edema following femoral vein ligation in thrombophlebitis is described. The great advantage of the anticoagulant method is that thrombosis and phlebitis are controlled in all parts of the body and not just in the legs. Patients with thrombophlebitis should not be kept in bed too long. In arteriosclerotic disease of the extremities, patients are encouraged to walk at a leisurely pace from one to three miles daily, and other activities such as dancing, golf, and riding a bicycle, are advised within reasonable limits. These exercises seem indicated because the active use of a muscle tends to produce an increase of its blood supply. When amputation is indicated, mid-leg amputation, rather than amputation above the knee, is advised in nearly all cases because of the greatly reduced mortality. In the management of the patient with thromboangiitis obliterans, tobacco must be given up completely and permanently. The author believes that amputations for this disease could be absolutely eliminated if thromboangiitis were always recognized and treated in its early stages and if patients cooperated by ceasing to use tobacco when instructed to do so.

NAIDE.

Eisen, Herman N.: Primary Systemic Amyloidosis. Am. J. Medicine 1:144 (Aug.), 1946.

Two case reports of primary systemic amyloidosis are presented with detailed autopsy findings and a review of the literature. In each patient the presenting manifestations were macroglossia, profound asthenia, and, ultimately, death in congestive heart failure.

Analysis of the symptomatology of forty-eight cases revealed that congestive heart failure occurred in 54 per cent and macroglossia and asthenia in 42 per cent.

In forty-six autopsied cases amyloid was found in the myocardium in 85 per cent and with somewhat less frequency in the endocardium (61 per cent), pericardium (48 per cent), valves (37 per cent), and in other organs.

Although exceptions occur, primary amyloid disease is characterized chiefly by involvement of the heart, tongue, gastrointestinal tract, and skeletal muscle. It affects middle-aged or elderly individuals, begins insidiously, is slowly progressive, frequently gives a negative Congo red test, and is not associated with chronic infection. Diagnosis is best established by biopsy but difficulty may be encountered in that the amyloid deposits have a variable affinity for the amyloid stains.

The age incidence, organ incidence, and atypical staining properties of the amyloid deposition associated with multiple myeloma resemble closely that seen in primary amyloidosis. In the latter, however, there is no hyperglobulinemia.

In contrast, amyloidosis secondary to chronic infection is characterized by a relatively high incidence of involvement of the kidney, spleen, liver, and adrenals, and only rarely the heart, tongue, gastrointestinal tract, or skeletal muscle. Also secondary amyloidosis runs a shorter course, occurs most frequently in young adults and rarely in middle life, and yields more consistent and typical results with the amyloid dyes.

The pathogenesis of the disease is unknown.

FRIEDLAND.

Silverman, S.: Vascular Tumours of the Spinal Cord Associated With Skin Hemangiomas. *Brit. M. J.* 33:307 (April), 1946.

A case is described of a vascular extradural spinal cord tumor, at the level of the sixth to tenth thoracic segments, in a woman 47 years old, who also had a very extensive congenital nevus, involving the fifth cervical to tenth thoracic dermatomes on the left side. The presence of the tumor was confirmed by operation.

The possibility of the presence of a vascular abnormality in the corresponding segment of the spinal cord should be kept in mind in patients who present a nevus of the skin together with signs and symptoms of a spinal cord lesion. Although malformations of the spinal cord, similar to and usually in the same segment as that of the skin condition, may be present, as a result of disturbance of mesenchymal development, their presence may not be suspected until either hemorrhage occurs or they increase in size, as in the case described.

Cases of vascular tumors of the spinal cord associated with skin hemangiomas which have been recorded in the literature are reviewed. Most of them are of a simple hemangiomatosis nature, corresponding to the skin condition, rather than hemoblastomatous.

NAIDE.

Falconer, M. A., and Lindsay, J. S. B.: Painful Phantom Limb Treated by High Cervical Chordotomy. *Brit. J. Surg.* 33:301 (April), 1946.

Pain occurring in a phantom limb has the same characteristics as causalgia occurring in an intact limb with a peripheral nerve injury. There are two main groups of cases. In one group pain impulses appear to arise in or around the neuromas or the divided nerves and can be relieved by excision of the neuromas or by sympathetic block or by sympathectomy. In the other group, painful impulses arise in the dorsal horn cells of the spinal cord and can be relieved only by section of the spinothalamic tract or by excision of the sensory cortex of the cerebrum. Infiltration of the appropriate peripheral or sympathetic nerve pathways with a local anesthetic solution is a useful diagnostic procedure for distinguishing clinically between these two groups. When these diagnostic tests fail to give relief, section of the spinothalamic tract is indicated and seems preferable to ablation of the sensory cortex, because it does not destroy the phantom or the patient's appreciation of his stump, but only abstracts from it the sensation of pain.

Two cases are described which illustrate these points. In both patients an arm was amputated above the elbow, as the result of wounds by a shell in one patient and by a bullet in the second. In both patients a cut was made in the cervical cord between the first and second cervical nerve roots to a depth of 4 millimeters. The phantom limb pain was completely relieved. There was no subsequent loss of sensation of touch, posture, vibration, or two-point discrimination. In each patient the only disability that remained was the loss of the limb.

NAIDE.

Bates, Robert R.: Surgical Aspects of Trench Foot. Surg. Gynec. & Obst. 83:243 (Aug.), 1946.

The author's experience with 264 cases of trench foot which required surgery is recorded. Many additional patients who came under his care had only a temporary superficial gangrene of the skin of the toes which recovered spontaneously. Most patients lost only parts of several toes. Eleven, however, lost all toes of at least one foot and thirty-two lost some or all of the metatarsal heads as well. It was found useful to adhere to certain surgical principles. Surgery was delayed until all possible spontaneous recovery had occurred. This policy resulted in the saving of toes and feet. Grafted skin was found unsuitable for covering the stumps. The advantages of covering a stump with a flap of normal weight-bearing type plantar skin outweighed the advantages of retaining metatarsal heads. Contrary to general surgical opinion, removal of some or all metatarsal heads was found not to handicap the function of the foot too seriously. A postoperative reactive hyperemia on a traumatic basis is described and contrasted with postoperative cellulitis due to infection. Preoperative and postoperative active exercises help to prevent shortening of heel cords and correct fibrotic contracture of toes. A prosthesis designed to be part of a shoe insert, often combined with a longitudinal arch support, is described.

NAIDE.

Waife, Sholom O., and Pratt, Peyton T.: Fatal Mercurial Poisoning Following Prolonged Administration of Mercurophylline. Arch. Int. Med. 78:42 (July), 1946.

A case of fatal mercurial poisoning following prolonged administration of mercurophylline is reported. As far as the authors could determine, this is the first reported case of a mercurial toxic nephrosis with anuria and death which followed the usual course of repeated parenteral injections of mercurophylline. The patient was a 35-year-old woman with rheumatic heart disease and congestive failure, who received mercurophylline parenterally for six months and who developed an acute anuria which proved fatal in spite of bilateral decapsulation of the kidney. Post-mortem examination revealed nephrosis, hemorrhage in the ileum and colon, and focal areas of necrosis and hemorrhage in the liver. Mercury was found in the liver and kidney. Death was attributed to mercurial intoxication.

The problem of the treatment of anuria of this type is still unsettled. Large amounts of fluid are usually administered, although there is some evidence that restriction of fluid intake and bilateral renal decapsulation may be of value. This issue has recently been reopened by Peters who believes that the factor which inhibits the flow of urine is an increase in intrarenal pressure and not a low arterial pressure or tubular blockage by detached necrotic cells.

BELLET.

Smirnova-Zamkova, A. I.: Significance of Basic Argyrophil Substance in the Pathogenesis of Hypertension. Am. Rev. Sov. Med. 3:534 (Aug.), 1946.

The argyrophil substance which enters into the composition of the hematoparenchymal barrier is stated to be a part of the physiologic connective tissue. It is situated between the epithelial structures and the subjacent connective tissue, as well as in the vascular walls, and forms an outer and inner filtering membrane. This substance exists in both a sol and a gel state and is able to pass from one state to the other in the presence of disease processes.

Studies were made on a series of twenty-five human subjects with hypertension and twelve rabbits in which experimental hypertension had been produced. Following silver impregnation of the vascular tissues, certain changes in the basic argyrophil substance were found. The media of the small vessels and the capillaries became permeated by thickened argyrophil membranes. Stenosis of the lumen occurred in advanced cases. The argyrophil filtering membranes of capillaries, small veins, and arterioles were condensed, thickened, and coarsened. This was most evident in vessels of the heart, lungs, and in the vasa vasorum. The changes are considered characteristic of the pathomorphology of hypertension. In the large vessels, coarsening of these membranes was more marked in the adventitia. Early in the course of hypertension, the condensation and thickening of the argyrophil fibers may dissolve; in the final stage of hypertension, generalized

fibrosis takes place and the organs shrink following the extensive condensation of the basic argyrophil substance. The changes occurring in the experimental animals and man were identical. The author views these changes as a causative factor in hypertension. BELLET.

Homans, J.: The Late Results of Femoral Thrombophlebitis and Their Treatment. New England J. Med. 235:249 (Aug. 22), 1946.

Femoroiliac thrombophlebitis is the usual end stage of thrombosis of the deep veins of the leg. Patients may be classified into five groups according to the following clinical criteria. In Groups 1 and 2, the predominant characteristic is edema, with or without pigmentation, induration, or ulceration. Local allergic inflammation and saphenous varicosity are often contributing factors. These patients are best treated by rest, elevation of the limb, muscular exercise, semi-elastic stockings, local treatment of the skin and nails, and, in some instances, by section or excision of varicose veins. The use of sclerosing injections is considered to be uniformly harmful. In Group 3 a pain complex, with or without associated vasomotor changes of the skin and stocking-like parasthesias, is the predominant characteristic. Lumbar sympathetic block is effective. Sympathectomy may be employed in obstinate cases. In Group 4, the outstanding feature is marked venous congestion, with cyanosis and prominent surface veins. Contrary to views widely held in the past, the author finds surgical division of the deep veins a highly useful procedure. Group 5 has as its chief characteristic recurrent thrombosis of the deep veins. Such episodes may last for a period of years. The therapeutic procedure of choice is ligation of the common iliac vein. KAY.

Russakoff, A. H., and Katz, H. W.: Dextrocardia and Bronchiectasis. New England J. Med. 235:253 (Aug. 22), 1946.

The authors re-emphasize the observation that congenital dextrocardia is not always a completely benign disorder. References are cited to indicate that bronchiectasis is present in from 16 to 23 per cent of these patients, and that chronic sinusitis occurs with unusual frequency. They report two cases of dextrocardia with bilateral bronchiectasis, chronic sinusitis, and transposition of the abdominal viscera. KAY.

Houston, C. S.: The Effect of Pulmonary Ventilation on Anoxemia. Am. J. Physiol. 146:613 (July), 1946.

Normal subjects breathed a mixture of approximately 10 per cent oxygen in nitrogen. Respiratory minute volume, arterial oxygen saturation, alveolar and arterial pO_2 and pCO_2 , and arterial pH were measured. Each subject was required to breathe a given oxygen mixture at several different levels of minute volume. It was found that the arterial oxygen saturation could be increased significantly by voluntarily increasing the minute volume. For example, one subject's arterial oxygen saturation was 64 per cent while breathing the low oxygen mixture at a rate of 10 liters per minute; at 17.5 liters per minute the arterial oxygen saturation rose to 85 per cent.

At the higher levels of ventilation, alveolar and arterial pO_2 and arterial pH rose, whereas alveolar and arterial pCO_2 fell.

It is suggested that the influence of changes in pulmonary ventilation must be evaluated in any clinical study of anoxia. FRIEDLAND.

Goldberger, E.: Significance of Downward T Wave in Precordial Leads of Normal Children. Am. J. Dis. Child. 71:618 (June), 1946.

Four-lead electrocardiograms were taken on 50 normal children and the group that showed T-wave inversion (18 per cent of the 50) were selected for further investigation. This group was studied by the use of six precordial leads taken with the author's indifferent electrode of zero potential. Precordial leads that faced the epicardial surface of the right ventricle showed either a positive or negative T wave which was associated with an RS type of ventricular complex. Leads facing the epicardial surface of the left ventricle showed a positive T wave only, which was usually

associated with a qR or qRs type of ventricular complex. A qR pattern associated with a downward T wave in a precordial lead is regarded as being always abnormal.

There is presumably more right ventricular surface facing the chest wall in childhood and this is believed to account for the greater frequency of T-wave inversion in the electrocardiograms of normal children.

HAUB.

Rosenkrantz, J. A., and Bruger, M.: Experimental Atherosclerosis: II. The Effect of Prolonged Feeding of Egg Yolk Powder in Rats. Arch. Path. 42:81 (July), 1946.

The feeding of egg yolk powder to rats for prolonged periods produced hypercholesteremia but no atherosclerosis. The authors suggest that lecithin, because of its choline content, inhibited the deposition of cholesterol in the aorta. The cholesterol and fat content of the liver were increased. To explain this discrepancy in the protective action of lecithin against lipid deposit in the aorta and its failure to protect the liver, the authors postulate that a diet consisting wholly of egg yolk powder is inadequate in those substances, such as are found in yeast or other sources of vitamin B complex, which ordinarily act to protect the liver.

The rats fed egg yolk powder failed to show an increase in systolic blood pressure or any evidence of vascular damage.

GOULEY.

Deutsch, A., and Lundin, G.: The Effect of Minute Amounts of Barium on Cardiac Muscle. Acta. Physiol. Scandinav. 11:373, 1946.

Small amounts of barium salts had a striking effect in initiating contraction in a threaded frog heart muscle preparation after a brief period of increased excitability. The contractions lasted several minutes. Strontium had about one-fiftieth the activity of barium, while other metallic ions had none. Calcium and magnesium salts increased the strength of contraction, while sodium salts diminished or abolished it. Adenosine triphosphate was found to be inactive in increasing the excitability of heart muscle in contrast to its recognized effect on skeletal muscle. Reports of its cardiac muscle action were occasioned by the use of its barium salt and the effect is now believed to have been due solely to the barium.

SAYEN.

Lundin, G.: The Influence of G-Strophanthin on the Mechanical Properties of Cardiac Muscle. Acta. Physiol. Scandinav. 11:221, 1946.

The action of G-strophanthin on normal heart muscle was studied in a parallel threaded frog ventricular muscle preparation. The contraction of the muscle, held between silver tweezers which served as the stimulating electrode, was measured by a condenser myograph. It was found that the drug had no effect on diastolic tension, extra tension during contraction, stiffness at rest and during contraction, viscosity, or the capacity for work during isometric contraction.

SAYEN.

Griffith, G. C., and Huntington, R. W.: Sudden Death in Rheumatic Fever. Ann. Int. Med. 25:283 (Aug.), 1946.

The present report concerns three cases of sudden death which occurred among a group of 7,165 patients with active rheumatic fever at the active rheumatic fever unit of the United States Naval Hospital at Corona, Calif. The three deaths were sudden, unexpected, and dramatic. Histologic studies showed unquestionable evidence of active rheumatic carditis.

A common and striking feature of the three cases was the presence of destructive lesions at the base of the aorta. In two of the cases there was unequivocal evidence of widespread vascular disease, particularly in the coronary and pulmonary arteries. Most of the changes appeared to be relatively acute.

It is believed by the authors that the cause of abrupt death in the three cases was due to an acute and anaphylactic coronary angiitis superimposed upon a low-grade rheumatic carditis.

WENDKOS.

Gold, M. M. A.: Congenital Dilatation of the Pulmonary Arterial Tree: Relation to Ayerza's Disease and Primary Pulmonary Arteriosclerosis. Arch. Int. Med. 78:197 (Aug.), 1946.

Congenital dilatation of the pulmonary artery as a single lesion unaccompanied by other developmental anomalies appears to be an extremely rare condition. It is referred to by this author as "isolated congenital dilatation of the pulmonary arterial tree." Its diagnosis is based on the following criteria: dilatation of the entire pulmonary arterial tree with or without sclerosis; hypoplasia of the aorta; absence of other congenital anomalies; absence of other primary disease of the heart, lungs, or arteries. When these criteria are applied, only four cases in the literature meet the requirements for the diagnosis of congenital dilatation of the pulmonary artery.

A case is reported which meets the above criteria. The patient was a 41-year-old white woman who had had two attacks of circulatory failure seven years prior to admission. Four years prior to admission she first noticed cyanosis of the fingertips. Physical examination on admission revealed cardiac enlargement, a systolic thrill over the entire precordial region, and a systolic murmur to the left of the sternal border. The electrocardiogram showed right axis deviation. Fluoroscopic examination revealed dilatation of the pulmonary artery, increased pulsation of the pulmonary vessels, and hypertrophy of the right ventricle. The temperature increased to 102°, and a blood culture was positive for *Streptococcus viridans*. The clinical diagnosis was bacterial endocarditis and patent ductus arteriosus. Necropsy showed right ventricular hypertrophy. The pulmonary artery was enlarged and its branches were dilated. Arteriosclerotic changes were found throughout the entire pulmonary arterial tree. Large numbers of the smaller vessels showed concentric fibrous thickening of the intima. From the description, this case may be considered to represent one of three conditions: Ayerza's disease, primary pulmonary arteriosclerosis, or isolated congenital dilatation of the pulmonary artery. The author points out that some of the cases reported as Ayerza's disease are merely examples of secondary sclerosis of the pulmonary artery, others are instances of primary pulmonary arteriosclerosis, and a few are cases of congenital dilatation of the pulmonary arterial tree. BELLET.

Orning, K., Sommerfelt, C., and Fredriksen, W.: Electrocardiographic Findings in Patients with Peptic Ulcers. Acta. Med. Scandinav. 124:564, 1946.

Among 579 patients with peptic ulcer but without heart disease (63 per cent of whom were men), electrocardiography showed sinus bradycardia to be common, especially in men below the age of 40. In women the rate was rarely less than 45 per minute but in men rates in the high thirties were not infrequent. Sinus arrhythmia was relatively more common in women and usually was associated with bradycardia. The most striking electrocardiographic feature was a high T wave (greater than one-half the height of the R wave in at least two leads) which occurred in 60 patients (52 of whom were men). Occasionally the T wave attained a height of 0.9 centimeter. The S-T segment was elevated in 37 of the 60 patients, especially in Lead II. Nine patients showed top-normal or slightly prolonged P-R intervals. Belladonna and diet caused partial or complete disappearance of the above changes in almost all cases, and the authors believe that the changes were the result of vagotonia.

In 74 cases in which hemorrhage had occurred, 35 per cent had "pathologic" tracings. The changes consisted chiefly of flattened T waves and depressed RS-T segments in Leads II and III without QRS changes. These appeared too promptly to be attributed to the relatively slight anemias that were present, and none of the patients had a significant fall in blood pressure. The changes were thought due to a vasomotor reflex affecting the coronary circulation, with consequent myocardial anoxemia. SAYEN.

Munek, W.: The Pathological Anatomy of Sudden Heart Death. Acta Path. et Microbiol. Scandinav. 23:107, 1946.

Of 500 cases of sudden cardiac death subjected to legal autopsy at Copenhagen 82 per cent were males. The author believes this figure to be of little significance since more men than women die under conditions of interest to police or insurance companies. The general Danish mortality

statistics report an approximately equal incidence of cardiac deaths in the two sexes. In 79.2 per cent of the cases, death was associated with coronary disease and its sequelae. Syphilitic aortitis accounted for 11 per cent; the majority of such cases showed no myocardial change. Valvular disease, usually aortic stenosis, appeared to be the cause of sudden death in 3.8 per cent and congenital defects in 1.8 per cent, while myocarditis was comparatively rare.

Of the patients with coronary disease, one-fifth showed no myocardial change and no arterial occlusion. Another 35.6 per cent showed thromboses, three-fourths of these being in the left coronary artery, in which the commonest sites of occlusion were in the first 2 centimeters of the left anterior descending ramus. The right coronary artery was usually occluded farther from its origin. Occlusions of the left circumflex branch were uncommon. Acute infarction was found in 18.7 per cent of the coronary group, almost one-half of these being associated with previous scarring. Two-thirds of the infarcts were anterior. The frequency of strenuous exertion preceding infarction is stressed. Most trombi had formed on atheromatous ulcers, but a few were associated with mural hemorrhage. Cardiac rupture occurred in 26 cases. Of these, 15 were on the anterior and eight on the posterior aspect of the left ventricle, while three were in the right ventricle. The author was impressed by the frequency of atheromatous changes in the coronary arteries in persons over 40 years old. These changes were most marked in the left anterior descending ramus where the process seemed relatively more advanced than in the aortic wall or the arteries of the brain.

SAYEN.

Burdick, D. L., Phelps, McK. L., and Peterson, M. C.: Anesthesia for Sympathectomy in Hypertension. N. Y. State J. Med. 46:2139 (Oct.), 1946.

With the more extensive surgery now being employed for sympathectomy, in hypertension, responsibility for the anesthetic management becomes proportionately greater. The present tendency is toward a more radical surgical procedure which may include the removal of ganglia as high as the third or fourth dorsal. It has become almost a matter of certainty that at some stage during surgery, the parietal pleura will be entered. The administration of the anesthetic must be planned with the anticipation of an open thorax and a collapsed lung. The present trend favors minimal medication with depressant drugs to permit spontaneous breathing, except when the controlled method is indicated. Use of the endotracheal technique is important, the choice between the oral or nasal route is not. A period of hypoxia, or actual anoxia, attendant upon a difficult or traumatic intubation is a serious complication.

Both during and following surgery, especially after the second stage, episodes of circulatory depression are not infrequently observed. At this period the development of pulmonary edema should be anticipated and measures taken for its prevention and treatment.

Neosynephrine continues to be the most valuable remedy for blood pressure disturbances. These authors believe that the prevention of sudden, severe hypotension in certain stages of the operation may be accompanied by starting an infusion of 5 per cent glucose in water or saline as soon as the patient is placed in the operating position. Neosynephrine, 0.02 Gm. per liter, is added to the solution, and the flow started at approximately 60 drops per minute. Regulation of the rate of flow permits a flexible means for controlling the amount of drug given in accordance with the varying needs. This method maintains a fairly even blood pressure throughout surgery and during the immediate postoperative period. At the conclusion of the continuous intravenous, neosynephrine, 0.0013 Gm. (2 minims) is given and repeated as needed if severe hypotension occurs. The authors believe that the administration of large amounts of plasma, a procedure frequently employed in the operating room, is contraindicated because the physiologic disturbances incident to sympathectomy are not due to any appreciable loss of circulating fluid from the body but to the dilatation of a considerable portion of the vascular bed, which can be controlled adequately by sympathomimetic drugs until the body mechanisms become adequately adjusted.

BELLET.

Schlichter, J. G.: Experimental Medionecrosis of the Aorta. Arch. Path. 42:182 (Aug.), 1946.

The author produced experimental medionecrosis of the aorta in dogs by coagulating the adventitia of the ascending aorta with heat. The site of coagulation was that area of the ascending aorta where anastomosis of the vasa vasorum from different main vessel origins is most pronounced. This was done in seven dogs weighing 20 to 30 pounds each. They were permitted to recover from the anesthesia and were killed in one, two, or six weeks.

In addition, a dog previously made hypertensive by daily injections of desoxycorticosterone acetate and prolonged drinking of 1 per cent salt solution, was similarly subjected to heat coagulation of the adventitia of the ascending aorta. This dog was killed in six weeks. Another hypertensive dog was used as a control.

A group of four dogs was studied six to twelve hours after coagulation. In all dogs the vasa of the aorta were injected and then examined by x-ray visualization.

In the dogs studied six to twelve hours after adventitial coagulation, there were no gross changes but microscopy revealed small hemorrhages in the outer third of the media. The inner third showed marked edema with separation of the elastic and muscle fibers. There was no cellular infiltration in the media.

One week after operation, the aorta showed yellowish brown areas in the media, not only beneath the coagulated adventitia but also 1 to 2 cm. distant from the area of coagulation.

Two to six weeks postoperatively, these yellow-brown areas were partially replaced by grayish areas which extended to the intima. One dog, whose postoperative course was marked by apathy and anorexia showed at autopsy a dissecting aneurysm of the ascending aorta with rupture 2 cm. above the aortic cusps.

At the end of one week, microscopy showed diffused necrosis of the outer and middle thirds of the media, evidenced by loss of nuclei and swelling of the elastic fibers. Areas of liquefaction with cyst formation with or without mucoid material were observed. Uneven involvement was attributed to anastomotic preservation of small blood vessels. In the second week, further loss of elastica was noted, and at the same time replacement of cystic and necrotic areas by young fibrous tissue and collagen deposit. This reparation process was pronounced in the sixth week. Fibrous tissue growing into the adventitia was richly vascularized. The changes in the hypertensive dog were the same, but the intimal thickening was much more marked. The control hypertensive dog showed no abnormal changes.

The author believes that the rich vascularization of the aortic adventitia prevents necrosis which occurs only when the entire circulation to a given area is destroyed. In the delayed subnecrotic response to this type of operation, the changes in the media are featured by cyst formations and mucoid degenerations. "Medionecrosis cystica idiopathica" has been ascribed by some workers to ischemia following circulatory disturbances of the vasa vasorum. The results of coagulation-necrosis of the aortic adventitia with destruction of many vasa vasorum is, according to Schlichter, a positive demonstration of the importance of the ischemia factor. GOULEY.

Farinas, P. L.: Retrograde Abdominal Aortography. A Contribution to the Study of the Abdominal Aorta and Iliac Arteries. Radiology 47:344 (Oct.), 1946.

Simple roentgen examination of the abdominal aorta and iliac arteries offers information only in the presence of calcification of the arterial walls or calcified aneurysms. Retrograde abdominal aortography is a simple method for the study of all the pathologic changes of the aorta and iliac arteries. This method consists in exposure of the femoral artery by blunt dissection under local anesthesia at the level of Scarpa's triangle and its puncture with a trocar 1.5 mm. in diameter through which are injected 50 c.c. of a 70 per cent solution of diodrast in two and one-half to three seconds. A tourniquet is applied at the root of each lower extremity in order to prevent the passage of the contrast medium into their arteries. With a trocar 1.5 mm. in diameter and a constant pressure of 15 pounds, it is possible to inject 25 c.c. of the opaque substance per second, the speed of injection being modified according to the blood pressure and vascular condition of the patient. The diagnosis of syphilitic disease of the abdominal aorta and iliac arteries is suggested by dilatation or occlusion of the lumen. Degenerative lesions are also frequently

observed by this method, which may disclose dilatation, elongation and tortuosity, including complete obliteration of the lumen. This author believes he is the first to have demonstrated valvular kinks in the iliac and femoral vessels which retard the circulation considerably. Surgical removal of these valvular kinks was shown to benefit greatly the circulation of both extremities. He hopes that this procedure will contribute to a better knowledge of the pathologic condition of these vessels and thus offer new approaches to treatment.

BELLET.

Schwarz, G. S.: Determination of Frontal Plane Area from the Product of the Long and Short Diameters of the Cardiac Silhouette. Radiology 47:360 (Oct.), 1946.

The material upon which this study was based consisted of 99 teleroentgenograms made on 93 subjects. Group I consisted of 25 films of normal subjects (10 males and 15 females) ranging in age from 7 to 54 years; in weight from 18 to 118 kg., in height from 132 to 177.5 cm., and in cardiac area from 72 to 145.5 square centimeters. Group II consisted of 74 films made on 68 subjects in whom clinical or x-ray evidence indicated heart disease. Thirty-five were males and 33, females. The ages varied from 6 to 82 years, the weight from 14.1 to 88.9 kg., the height from 100 to 185 cm., and the cardiac area from 50 to 282 square centimeters.

The films were made with the subject standing or sitting facing a vertical cassette changer and with a target film distance (D) of approximately 6 feet. The silhouettes were outlined with wax pencil on the film and then transferred to semitransparent paper for planimetric measurement of area and linear measurements of the long and short diameters. For each case the product of these diameters was divided into the area of the silhouette, the quotient being a factor which is indicated as F. For the normals the mean value of F was 0.740; for the abnormals, 0.730; the average 0.735 was therefore chosen as the factor for general application. On this basis the calculation of frontal plane area from long and short diameter becomes

$$A = L \times S \times 0.735$$

where A is the gross frontal plane area of the heart in sq. cm. in full-sized roentgenograms made with the patient facing the film at a target-film distance of approximately 72 inches; L, the long diameter of the cardiac silhouette in cm.; S, the short diameter of cardiac silhouette in centimeters.

Investigation of the accuracy of this formula revealed the maximum deviation to be -4.7 per cent and +6.5 per cent, the minimum deviation zero. This indicates that the formula $L \times S \times 0.735$ is more accurate than the ellipse formula. Three monograms are provided to facilitate application of the various formulas. These yield net frontal plane area and also the amount by which this value varies from normal.

BELLET.

Hodges, P. C.: Heart Size from Routine Chest Films. Radiology 47:355 (Oct.), 1946.

The systolic size rarely is recorded on routine chest films and the larger shadow in a pair of such films may be accepted as of approximately diastolic size. Hodges measured the gross frontal plane area from the larger of the two shadows in routine chest films and then corrected this value for divergent distortion. If the net frontal plane area thus obtained is within plus or minus ten per cent of the normal area predicted from the patient's height and weight, it is reported as normal, with the actual percentage variation from normal added in brackets. Because of a divergent distortion that is always present in ordinary roentgenograms, gross area is greater than true or net frontal plane area, the latter being obtained from the former by multiplying gross area by a correction factor F, obtained from the equation:

$$F = \left\{ 1 - \frac{K}{D} - \frac{C}{3D} \right\}^2$$

In this equation, F is the divergent distortion correction factor; K, the distance in centimeters between anterior surface of chest and film; D, the distance in centimeters between target of x-ray tube and surface of film; C, the anteroposterior diameter of chest in centimeters (varies from approximately 5 cm. to 28 cm. depending upon the patient).

Computations would be far too tedious if they had to be done for each examination, but by reducing the various equations to alignment charts or nomograms, all computations are avoided. The author concludes that although the best way to determine the size of the frontal plane area is to measure it with a planimeter, without much sacrifice of accuracy, one may simplify the technique by measuring the long and the short diameters and multiplying their product by the factor 0.735.

BELLET.

Crosby, R. C., and Cooney, E. A. **Surgical Treatment of Ascites.** *New England J. Med.* 235:581 (Oct. 17), 1946.

The literature concerning omentopexy, nephrectomy with anastomosis of the renal pelvis to the peritoneum, and portocaval shunts in the treatment of ascites is reviewed. The authors describe five cases of portal cirrhosis and one of constrictive pericarditis in which the ascites was relieved by the insertion of a hollow glass button into the lower rectus sheath so that ascitic fluid drained from the peritoneal cavity into the subcutaneous tissues and was absorbed as edema fluid. They were unable to ascertain the originator of this method. The need for repeated abdominal paracentesis and the attendant loss of protein was obviated. Four of the five patients with cirrhosis were greatly improved. Edema of the abdominal wall and thighs continued to be a troublesome sequel in the patient with constrictive pericarditis.

KAY.

Segall, E. L., Kurland, G. S., and Riseman, J. E. F.: **The Effect of Age on the Clinical Effectiveness of Nitroglycerin Tablets.** *New England J. Med.* 235:650 (Oct. 31), 1946.

Current medical opinion recommends that patients employing nitroglycerin for the treatment of angina pectoris discard old tablets and purchase fresh ones every three to six months. The controversial results of chemical assays of nitroglycerin tablets at varying times after manufacture are cited. The authors performed biologic assays of fresh tablets, of tablets stored at room temperature for periods as long as eleven years, of tablets incubated at 37°C. for three months, and of tablets contained in loosely-capped vials carried in vest or trousers pockets for a period of four months. The test subjects were patients with angina pectoris. For each patient the amount of exercise required to induce pain was a known constant, which could be measurably increased after the sublingual administration of nitroglycerin. As a result of this study the authors conclude that there is no essential loss of clinical potency in old tablets stored at room temperature for many years, or of tablets carried by patients in the customary manner for four months, but that fresh tablets stored for three months at 37°C. become completely ineffective clinically.

KAY.

Dean, J. V. B.: **Relation of Cardiac Enlargement to Hypertension in Acute and Chronic Glomerulonephritis.** *Am. J. Med.* 1:161 (Aug.), 1946.

The author reemphasizes the absence of a correlation between heart size and arterial blood pressure in patients with chronic glomerulonephritis. The cardiothoracic ratios of three normotensive patients with chronic glomerulonephritis varied between 0.55 to 0.64 over eight to nineteen years of observation. On the other hand, the cardiothoracic ratios of three hypertensive patients with chronic glomerulonephritis remained at 0.51 or less over a two- to five-year period of observation. In these latter patients the cardiothoracic ratios did not reach or exceed 0.50 until their disease had progressed to its terminal phase.

It is concluded that cardiac enlargement in patients with long-standing chronic glomerulonephritis is not necessarily related to coexisting hypertension.

FRIEDLAND.

Pardee, H. E. B., and Goldenberg, M.: **Electrocardiographic Features of Myocardial Infarction as Affected by Involvement of the Septum and by Complete and Incomplete Transmural Involvement.** *Arch. Inst. cardiol. México* 16:109, 1946.

The authors believe that many of the current theories regarding the cause of electrocardiographic changes after myocardial infarction need revision. They therefore reviewed the clinical

records and autopsy findings of 11 patients who died soon after a myocardial infarction, and one patient who died two years later. This study led to the following conclusions:

1. Rotation of the electrical axis of the QRS complex toward the right may occur after either anterior or posterior infarction but occurs more uniformly after the latter.
2. The typical S-T and T-wave changes occur most often when necrosis of either the anterior or the posterior wall is associated with a lesion of the septum. When the septum is undamaged, the typical changes occur less constantly.
3. The typical S-T and T-wave changes in both the limb and precordial leads and the QRS complex changes in the precordial leads may appear occasionally after anterior infarction even if the subepicardial layers are unaffected; usually, however, there is definite evidence of involvement of the subepicardial layers.
4. A Q or Q-S wave in the precordial leads is associated with necrosis of the anterior part of the septum. It may be present when the latter is not accompanied by involvement of the anterior wall.
5. A complete transmural lesion may be accompanied by a deep Q wave in Lead III even without involvement of the posterior part of the septum.
6. The records of cases with anterior infarction but no subepicardial necrosis resemble those seen after exercise and anoxemia tests and during anginal attacks.

LUISADA.

Fox, T. T., Sokol, D. D., and Bernstein, I. J.: The Significance of Concordant Inverted Initial Ventricular Deflections in the Electrocardiogram of Patients With Pulmonary Tuberculosis. *Quart. Bull. Sea View Hosp.* 8:95 (April), 1946.

The significance of electrocardiograms which show concordant QRS complexes is not clear. Some believe these to be the result of myocardial damage occurring either alone or in association with rotation of the heart around its longitudinal axis. These authors observed fourteen patients who exhibited this condition. In twelve of these the concordant feature was caused by S waves. In two patients, the concordant downward deflections were caused by Q waves; these two patients had had acute coronary occlusion. There were three more cardiacs in this group of fourteen patients; one with evidence of impairment of the conduction mechanism, one with radiographic evidence of heart enlargement, and a third with hypertension.

In evaluating the significance of the downward QRS deflection it is essential to differentiate between the Q and S type of electrocardiogram. It is the conclusion of these authors that the presence of concordant downward deflection of the QRS group caused by S waves is neither an indication of heart disease nor of prognostic significance. Spontaneous and artificially produced variations in the form of the QRS complexes in some of the cases speak in favor of the phenomenon being a function of the position of the heart within the thorax. The Q-type of tracing is usually indicative of a coronary occlusion, and has a definite prognostic value.

BELLET.

Stokes, W.: The Effect of Nitrites and Exercise on the Inverted T Wave. *Brit. Heart J.* 8:62 (April), 1946.

In practice, the similarity of the T_1 type of cardiac infarction and the inversion of the T wave from hypertension or aortic valvular disease presents a common problem in differential diagnosis. Observations were therefore made on the effects of nitrite and exercise on the inverted T wave in order to evaluate the help that such tests might afford in deciding this problem.

Forty-five patients whose electrocardiograms showed deformity of the T wave were studied. The electrocardiogram was recorded before and after (1) a standardized inhalation of amyl nitrite and (2) a standardized exercise test which consisted of bending repeatedly to touch the toes, or raising and lowering the legs with the knees straight while the subject reclined on a couch, the exercise being continued to the point of fatigue.

Amyl nitrite inhalation was followed by correction of inverted T waves in six of sixteen cases of cardiac infarction and seven of thirteen cases of hypertension but the T wave inversion was not corrected in any of seven cases of aortic valvular disease. Exercise similarly righted the inverted T waves in nine of sixteen cases of myocardial infarction and in two of thirteen cases of hypertension but did not correct the T wave inversion in any cases of aortic valvular disease.

It was concluded that tests involving amyl nitrite inhalation, exercise, or change of posture do not differentiate the T wave inversion of myocardial infarction from that of hypertension. It is not certain that these procedures alter the T waves by relieving myocardial ischemia since their effect in cases of hypertension is similar to that in myocardial infarction. LAPLACE.

Ellis, L. B.: Electrocardiographic Abnormalities in Severe Malnutrition. Brit. Heart J. 8:53 (April), 1946.

Serial electrocardiograms were made in a series of thirteen liberated American prisoners of war who had been starved by their German captors and whose condition was critical. Clinical examination revealed severe malnutrition but there were no definite manifestations of avitaminosis or anoxia of the heart muscle.

The cardiographic changes consisted of a marked prolongation of the Q-T interval, unusually well-marked but not persistent U waves, and, less constantly, depression of the S-T segment, alterations of the T waves, and increase in the P-R and QRS intervals.

It was concluded that the electrocardiographic changes in malnourished subjects probably represented a composite picture due to prolonged protein and carbohydrate starvation and electrolyte imbalance. The fact that the cardiograms returned to normal within two or three weeks after institution of adequate therapy suggests that the changes are chiefly due to functional and not to structural causes. LAPLACE.

Szekely, P.: The Action of Magnesium on the Heart. Brit. Heart J. 8:115 (July), 1946.

Magnesium appears to have a depressant action on the heart but there is no general agreement about the mechanism of this action and there are few reports dealing directly with the clinical application of its cardio-inhibitory properties. Observations were therefore made on the effect of intravenous injection of 20 c.c. of a 20 per cent solution of magnesium sulfate on the electrocardiogram in twenty-six cases in which the diagnoses included paroxysmal tachycardia, auricular fibrillation, and extrasystoles.

Magnesium produced only minor changes in the normal cardiogram. It affected nine of thirteen cases of paroxysmal tachycardia; in five of the nine cases, the effect was lasting and in four only temporary; in the remaining four cases, variable degrees of A-V block appeared. Extrasystoles caused by full digitalization were either completely obliterated or altered by magnesium sulfate while extrasystoles from other causes were not affected by it. Magnesium had no effect on auricular fibrillation.

It is concluded that magnesium in the dosage used in this study has no appreciable effect on the normal conduction system. It may depress impulse production in heterotropic centers and, in the presence of increased myocardial irritability, all parts of the conduction system may be depressed. The data presented justify the use of magnesium sulfate as a therapeutic agent in paroxysmal tachycardia; it is a safe procedure but its effect may be only temporary. LAPLACE.

Evans, W.: The Heart in Sternal Depression. Brit. Heart J. 8:162 (July), 1946.

The author studied sixteen patients who had depression of the sternum and had been referred because of supposed heart disease. In none of the patients, however, were the symptoms the result of cardiac enlargement or insufficiency. They were in all cases attributable to physical inactivity or anxiety resulting from unwarranted invalidism.

The cases were separated into three groups according to the degree of sternal deformity: funnel depression (two cases), cup depression (eight cases), and saucer depression (six cases). The radiological findings were characteristic for each group. In the presence of funnel depression which is the most marked deformity, the heart was displaced bodily to the left of the spine and was unchanged in size or shape. In the cases of cup depression, the cardiac silhouette in the anterior view was less dense than normal and was moderately enlarged with prominence of the pulmonary arc. In the left oblique view, the heart shadow was normal or small and was displaced backward to overlap the spine, thereby obliterating the clear areas of the aortic window and the

retrocardiac space. Similar effects, although less in degree, were observed in the saucer depression. The importance of this last group is that the chest deformity is less obvious, and the changes to which it gives rise lead to erroneous interpretation of the enlarged cardiac area seen on radiocopy if the effects of the saucer depression are not fully appreciated. None of the sixteen patients had any actual enlargement of the heart or suffered symptoms related to the heart. All were healthy and were handicapped only by the restrictions imposed on them by a medical examination that had misinterpreted the clinical and radiological signs.

LAPLACE.

Denolin, H.: The Electrocardiographic Criteria and Localization of Bundle Branch Block. The Present State of the Question. Acta Cardiologica 1: 44, 1946.

The present concept of bundle branch block is reviewed. The author believes that none of the usually proposed electrocardiographic criteria can be accepted as wholly reliable to establish a diagnosis of this lesion or particularly of ventricular asynchronism. He considers it impossible to locate the site of an intraventricular conduction defect on the basis of the classic electrocardiogram because of the number of factors which modify the electrical picture, including the situation of the heart in the thorax, intrathoracic contacts, and associated myocardial damage. He states that only a demonstration of asynchronism of electrical or dynamic phenomena can warrant a diagnosis of bundle branch block and its localization. It is suggested that the term "disturbance of interventricular conduction" should be used rather than bundle branch block because ordinarily the available diagnostic criteria comprise simply the electrocardiographic pattern and give no indication of the functional activity of the ventricles. Further study of ventricular asynchronism in patients who have bundle branch block and curves of axis deviation is required.

LAPLACE.

Priest, W. S., and McGee, C. S.: Streptomycin in the Treatment of Subacute Bacterial Endocarditis. J. A. M. A. 132:124 (Sept. 21), 1946.

In the treatment of subacute bacterial endocarditis with penicillin, these authors encountered four organisms which were highly or completely resistant to penicillin. One of these was the *Hemophilus parainfluenzae*; the other three organisms were streptococci. The *H. parainfluenzae* was apparently unaffected after many weeks of penicillin therapy in daily dosage up to 2 million units. Sulfamerazine also had no apparent effect in vitro. Cure resulted from the combined administration of penicillin in daily dosage of 500,000 to 1 million units and sulfamerazine in dosage sufficient to give a level in the blood of 0.8 to 11 mg. per cubic centimeter. The organism in this case was subsequently found to be sensitive in vitro to streptomycin. In a group of thirty-four patients, three strains of streptococci were encountered which were highly insensitive to penicillin. One was typically *Streptococcus viridans* after freezing but was rather atypical in primary cultures of blood. The other two were typical nonhemolytic streptococci.

In vitro sensitivity to penicillin ranged from 0.8 to 6 units per cubic centimeter. Sensitivity to streptomycin ranged from 0.1 to 1 unit per cubic centimeter. Streptomycin apparently produced sterilization of the valvular lesions in Case I, resulted in negative cultures of blood after penicillin therapy had failed in Case II, and was solely responsible for the cure obtained in Case III.

The dose of streptomycin used, 500,000 units (0.5 Gm.) per day, is not necessarily that which will be adequate in all cases in which use of the drug is indicated.

BELLET.

Gross, R. E., and Ware, P. F.: The Surgical Significance of Aortic Arch Anomalies. Surg., Gynec. & Obst. 83:435 (Oct.), 1946.

A brief resume is made of the more common anomalies of the aortic arch and the large arteries which arise from it. Many of the anomalies do not produce important symptoms, but others have considerable significance since they give rise to pressure on the esophagus and trachea, impose a burden on the heart because of an arteriovenous type of shunt, or lead to severe derangements in the circulation because of an obstruction in the aortic pathway.

In the first group of malformations the esophagus or trachea (or both) are impinged upon by (1) a right-sided aortic arch, (2) a double aortic arch, (3) a constricting ring of vessels (or remnants

thereof), or (4) an anomalous right subclavian artery. A right-sided aortic arch cannot be changed by surgical means, but if this abnormally placed structure is attached by a ligamentum arteriosum (or a patent ductus arteriosus) to the pulmonary artery so that this latter vessel is pulled back against the trachea on the left side of the esophagus, then division of the ligament (or of the ductus) should give some relief. When a double (or split) aortic arch gives respiratory distress, the patient can be greatly helped by cutting the anterior (left) limb. When dysphagia occurs from a right subclavian artery, which originates from the left side of the aortic arch, the symptoms can be abolished by dividing the artery so that it no longer presses on the esophagus.

While some individuals live a long and active life with a patent ductus arteriosus, particularly if it is a small one, statistics indicate that the average length of life is little more than half of the normal expectancy. While surgery can be deferred until symptoms have developed, the technical difficulties of operation at such times are considerable. In contrast, the closure of a ductus at an early age can be accomplished with a negligible risk, and hence operation is recommended in childhood or young adult life before complications have developed. Experience indicates that ligation of a ductus is usually satisfactory but that complete division of the vessel is more desirable because it insures complete interruption of the shunt and precludes any possibility of its re-establishment.

Individuals with a high degree of obstruction in the distal part of the aortic arch or in the first part of the descending aorta may live to advanced ages with little or no difficulty, but most of them develop serious or even fatal complications in mid-life, particularly hypertension with its sequelae. Experimental observations show that a section of the upper thoracic aorta can be excised and that the open ends of the aorta can be satisfactorily joined. Such a procedure has been adapted to human beings; a narrowed (or completely obstructed) segment of the aorta can be removed and the remaining ends of the aorta can be anastomosed. After performance of this operation, the hypertension is quickly relieved. Five patients with coarctation of the aorta have been operated upon with only one death. The fatality occurred in the first patient in whom the clamps were removed from the vessel too quickly, before adjustments could be made in the cardiovascular apparatus to the opening up of an enormous vascular bed in the lower part of the body.

NAIDE.

Dick, G. F., and Schwartz, W. B.: Experimental Endocarditis of Dogs. Arch Path. 42:159 (Aug.), 1946.

The authors studied the incidence of experimental endocarditis in dogs, with special reference to the type of the organism, its virulence, and its dosage. Intravenous injections four times weekly of cultures fortified by the addition of sterile dog blood resulted in the development of bacterial endocarditis in 61 per cent of twenty-six dogs. The organisms were various strains of *Streptococcus hemolyticus* and *Streptococcus viridans* isolated from the blood and urine of human patients. Beta hemolytic and viridans strains produced positive results with equal frequency and, contrary to existing opinion, previous damage to the heart valves was not essential. It was not necessary that the streptococci should come from human endocarditis; similar organisms from a great variety of human lesions were used with equal success. Organisms other than streptococci did not induce endocarditis in these dogs.

GOULEY.

Barnes, A. C., and Ervin, H. K.: The Effect of the Anticoagulants on Postpartum Bleeding. Surg., Gynec., & Obst. 83:528 (Oct.), 1946.

This study was undertaken to determine whether or not anticoagulants are contraindicated by vaginal bleeding post partum. Eleven patients who served as controls uniformly showed the marked elevation of prothrombin level which has been noted in a normal postpartum patient. Readings as high as 130 per cent were obtained (second day following delivery), and with the exception of one reading of 85 per cent on the third postpartum day, the hemoglobin did not fall below 100 per cent in any patient until after the fifth day. Fourteen postpartum patients were given dicumarol in doses adequate to depress their prothrombin levels to the therapeutic range. Five postpartum patients were given heparin in therapeutic doses.

Although the present series is not large, the patients were followed carefully and the authors were unable to find evidence that anticoagulants significantly increased peripheral blood loss. The customary precautions in connection with the use of these drugs should be scrupulously observed. The data obtained would indicate that heparin and dicumarol are not necessarily contraindicated in the postpartum patient. Although the blood loss in these patients was the same as that of the controls, two of them with episiotomy wounds developed hematomas, and one of these patients underwent a partial breakdown. Aside from this complication, the treated patients presented the same findings as did the control group.

Bleeding and clotting times obtained on the nursing babies showed prolongation in over one-third of the cases. These reactions were not consistent: in two cases, both were prolonged. In the other three, only the clotting time was increased. It is felt that these studies performed on toe or heel blood are not sufficiently delicate for the results to bear close scrutiny. In view of the report by Field, however, that rat litters nursed by dicumarolized females showed hemorrhagic tendencies, it might be wise to consider weaning a baby whose mother required prolonged medication with dicumarol.

NAIDE.

Shumacker, H. B.: The Surgical Treatment of Gangrene in Trench Foot. Surg., Gynec., & Obst. 83:513 (Oct.), 1946.

Superficial gangrene in trench foot does not present a serious problem. However, the great majority of patients with deep gangrene have infection of a mixed character. Although such infection is often controlled satisfactorily with sulfadiazine or penicillin and with the local application of warm saline compresses following the removal of gangrenous parts, organisms resistant to these drugs are commonly present.

Vasoconstriction, sometimes intense, was present in the majority of patients. It is thought that lumbar sympathetic ganglionectomy is a useful adjunct in the treatment of deep gangrene of trench foot and that it results in more speedy healing and in conservation of tissue. In the event that skin defects have resulted from the loss of parts, it is advisable to cover these areas with a split thickness or full thickness graft. If the ends of metatarsals are exposed, a graft of full thickness is generally necessary. The stump is satisfactory for standing or walking, if all the toes are removed, or even if parts of the metatarsal heads must be removed. If amputation must be carried out more proximally through the metatarsals, the stump is generally unsatisfactory. Pain on weight-bearing was not peculiar to the patients who had undergone amputations but occurred just as frequently in patients with trench foot who had had no gangrene at all.

NAIDE.

Kahn, J. W.: Thrombophlebitis of the Deep Veins in Thromboangiitis Obliterans. Surg., Gynec. & Obst. 83:449 (Oct.), 1946.

Two patients with thromboangiitis obliterans are reported in whom deep thrombophlebitis was the presenting symptom. One of the patients developed pulmonary infarction secondary to the thrombophlebitis. This is a rare complication in thromboangiitis obliterans. The arterial tree should be carefully investigated in all cases of afebrile, idiopathic, deep thrombophlebitis in young patients. The presence of passive congestion in a limb secondary to venous obstruction may cause a reactive hyperemia which temporarily may mask some of the signs and symptoms of arterial insufficiency.

NAIDE.

Berry, R. L., Campbell, K. N., Lyons, R. H., Moe, J. K., and Sutler, M. R.: The Use of Tetraethylammonium in Peripheral Vascular Disease and Causalgic States. Surgery 20: 525 (Oct.), 1946.

A new method of producing a blockade of autonomic ganglia by means of parenteral injection of tetraethylammonium bromide or chloride is reported. Acheson and Moe studied the action of tetraethylammonium and concluded that the responses of the nictitating membrane, the blood pressure, and the heart rate could all be explained by a blockade of autonomic ganglia, both sympathetic and parasympathetic.

In the present report, the results of the use of this compound in a variety of peripheral vascular diseases and causalgic states is described. The drug is administered intravenously or intramuscularly. The intravenous dose ranged from 100 to 500 mg. This was injected slowly in from fifteen to sixty seconds; significant changes in the volume of the pulse and the general reaction of the patient were used as guides to cease or delay further administration of the drug. Intramuscular injections were utilized to prolong the effect of the autonomic blockade only in patients under observation in the hospital. These were given in doses of less than 20 mg. per kilogram of body weight, 1.0 to 1.5 Gm., one-half the dose being administered in each buttock.

The intravenous administration produces a metallic taste in fifteen to twenty seconds and is followed by a sense of numbness and tingling in the extremities which is associated usually with a fall in blood pressure in hypertensive patients and a rise in heart rate. Sweating, if present, stops, the mouth becomes dry, and there is incomplete dilatation of the pupil with loss of accommodation. With the fall in blood pressure, there is an increase in skin temperature of the toes and fingers, usually within five minutes, which persists after the blood pressure returns to its initial level. Though the blood pressure in the supine position returns to its initial level, postural hypotension may exist in diminishing intensity for fifteen to sixty minutes. The vasoconstriction gradient is largely abolished so that the toe and thigh temperatures are equalized.

The effects of tetraethylammonium on peripheral blood flow were compared with the effects of lumbar sympathetic blocks, spinal anesthesia, local nerve block, and sympathectomy. This comparison was made both in patients with vascular disease and in a control group of relatively healthy individuals. In fifty-two of fifty-five comparative tests, tetraethylammonium proved equal or superior to the usually accepted methods of producing sympathetic block. The ease of administration is an additional highly desirable feature of tetraethylammonium, since spinal anesthesia is not always desirable or possible and paravertebral sympathetic block, even in expert hands, is not always successful.

Approximately 500 patients received tetraethylammonium bromide or chloride on one or more occasions, either as a diagnostic or therapeutic measure or both. The various diseases studied included hypertension, arteriosclerosis obliterans, thromboangiitis obliterans, Raynaud's syndrome, livedo reticularis, acrocyanosis, causalgic states including various types of reflex sympathetic dystrophy, superficial and deep thrombophlebitis with and without evidence of vasospasm, various types of lymphedema, post-traumatic edema, scleroderma, endarteritis, herpes zoster and post-herpetic neuralgias, and trench and immersion foot sequelae.

Tetraethylammonium has proved to be a satisfactory method of producing either a temporary or prolonged sympathetic block and is therefore useful in improving the circulation or ameliorating pain of circulatory origin.

The intravenous injection of this drug to produce autonomic blockade has been utilized daily as an outpatient procedure for eight months. No emergency hospitalization following the administration of this drug has been necessitated at any time. The patient is asked to refrain from driving his car from one to two hours because of loss of accommodation. The patient is usually unaware of any visual impairment. Adrenalin is specific in counteracting any untoward symptoms.

In the doses used in this study and in the patients reported here, no significant toxic effects were noted. In other cases reported elsewhere, complications of the injection were experienced. Some patients with very high blood pressure experienced a state of peripheral circulatory collapse following the intravenous injection which was quite transient in character and which responded to epinephrine. Other patients developed a state of dyspnea similar to that observed in hysterical hyperventilation. In a few patients, the sensations of weakness, fatigue, and light-headedness were very pronounced. The drug has been administered more than one thousand times to more than 500 patients in the doses indicated with very few alarming reactions.

NAIDE.

Chambers, William N.: Acute Myocardial Infarction. *New England J. Med.* 235:347 (Sept. 12), 1946.

The author observed 100 consecutive patients in their initial attack of acute myocardial infarction. Thirty-four patients died within the first thirty days, and an additional eight died

within one year. The average age of the 100 patients was 59 years; the average age of those who died was three years greater than of those who survived. The ratio of men to women was 3 to 1. The women of these series were older and had a higher mortality rate than the men. In eighty-four of the patients, dyspnea, anginal pain, or other symptoms of cardiovascular disease preceded the infarction. Hypertension was known to have existed in seventy-four of the patients and diabetes in thirteen. Pain, the most frequent symptom, occurred in seventy patients. Dyspnea, the second most prominent chief complaint, occurred in twenty-six patients. The most frequent physical findings were poor heart sounds and congestive râles, cyanosis, edema, tachycardia, fever, and disturbances in rhythm. These and other physical signs were considerably more prominent in those who died in the initial attack than in those who survived. Congestive heart failure was present on admission or subsequently developed in 65 per cent of the fatal cases. Pulmonary embolism occurred in six patients, five of whom survived. Cerebral hemorrhage resulted in death in one of the two patients in whom it developed. Other thrombotic or embolic complications are not described. Variations of blood pressure and of the leucocyte counts and sedimentation rates are described and correlated with mortality. Electrocardiographic tracings indicated anterior-apex infarctions in fifty-two patients, posterior-base infarctions in forty, and a combination of types in eight. Three months after the infarction, none of the tracings had returned to normal; after two years, thirty-eight patients had normal tracings.

Of the fifty-eight patients who survived one year, nine had had nonfatal recurrent infarctions. Of the other forty-nine, half had angina pectoris, eight had some symptom of cardiac insufficiency, and eleven were without symptoms. About half of these patients were working full or part time.

KAY.

Brun, C., Knudsen, E. O. E., and Raaschou, F.: Kidney Function and Circulatory Collapse. Post-Syncopal Oliguria. J. Clin. Investigation 25:568 (July), 1946.

Circulatory collapse was induced in healthy, water-loaded subjects by placing them in the passive erect posture on a tilt table at an angle of 40 to 60 degrees with the horizontal plane. After symptoms and signs of collapse appeared, the subjects were returned to the horizontal position with immediate restoration of the circulation to normal, as judged by the pulse, blood pressure, and subjective symptoms. Hematocrit, blood viscosity, and plasma proteins increased to levels above control values as the passive erect position was maintained, but no conspicuous changes in urine flow were observed until collapse intervened. Oliguria then occurred and persisted fifteen to ninety minutes after the subjects were returned to the horizontal position. During the period of post-syncopal oliguria, urinary specific gravity rose from low values to 1.020 to 1.025, and the hematocrit, blood viscosity, and plasma proteins gradually returned to control levels. In the immediate post-syncopal period, inulin clearance (glomerular filtration rate) and diodrast clearance (effective renal plasma flow) were reduced to 70 and 75 per cent, respectively, of their control values but for only a fraction of the total period of oliguria.

The absence of persistent reduction in glomerular filtration suggested that the oliguria was due to the presence in the circulating blood of an antidiuretic substance which caused increased reabsorption of water by the renal tubules. This hypothesis was examined by transfusing into water-loaded, supine subjects heparinized blood obtained from post-syncopal donors. The post-transfusion oliguria obtained lasted thirty to forty-seven minutes and was accompanied by increased concentration of urinary chloride. Blood obtained from control subjects exerted no similar effect, but the administration of five international units of posterior pituitary substance reproduced the oliguria and the increased urinary chloride concentration, and further resembled post-syncopal oliguria in that total urinary chloride tended to diminish somewhat.

The reduced output of total urinary chloride observed in these experiments was not in accord with the results of other investigators but the authors explained this discrepancy on the basis of prior negative chloride balance induced in their subjects by the water diuresis.

Two patients with diabetes insipidus developed distinctly less prolonged post-syncopal oliguria and it was postulated that these individuals possessed less ability to produce antidiuretic hormone.

It is intimated that the effective stimulus for the secretion of antidiuretic hormone may be either cerebral anoxia or reflexes mediated through the pressor receptors. It is also suggested

that the oliguria seen in other types of circulatory insufficiency, such as cardiac insufficiency, diabetic coma, and shock, may be associated with this mechanism. FRIEDLAND.

Ogura, J. H., Fetter, N. R., Blankenhorn, M. A., and Glueck, H. I.: Changes in Blood Coagulation Following Coronary Thrombosis Measured by the Heparin Retarded Clotting Test (Waugh and Ruddick Test). J. Clin. Investigation 25:586 (July), 1946.

This study was motivated by a previous study in which one of the authors found auricular or ventricular mural thrombi in 65 of 100 cases of coronary thrombosis which were studied post mortem. The Waugh-Ruddick technique was applied to the blood of patients admitted to the hospital with unquestionable findings of coronary thrombosis. The technique consists of recording and plotting the coagulation time of blood in a series of nine tubes to which increasing quantities of heparin are added. With coagulation time plotted on the ordinate and tube number on the abscissa, an acceleration is demonstrated by "flattening of the curve," i. e., the greater the blood's coagulability, the faster the coagulation time. In the tube (No. 9) containing the largest quantity (7/10 unit) of heparin, the coagulation is slowest; small differences in coagulation time are magnified.

Twenty-one of twenty-seven patients with coronary thrombosis were found to have accelerated coagulation commonly by the third day and usually by the twelfth day. In twenty-three there was a return to normal by the end of the third week.

Control patients showed some acceleration of coagulation after their third day in bed, but the acceleration was not as pronounced as it was in patients with coronary thrombosis. There is a suggestion that thrombo-embolic complications may be associated with acceleration of coagulation. In six patients with coronary thrombosis who were receiving digitalis, the data do not suggest that digitalis accelerates coagulation. Neither did xanthines influence the coagulation curve.

In view of the delay in the acceleration of coagulation until the second or third day after the onset of coronary thrombosis, the data indicate that accelerated coagulability is not a cause of coronary thrombosis but is rather a result of the thrombosis and the possible release of thromboplastin by the subsequent tissue damage.

It would appear that early anticoagulant therapy may prevent the formation of mural thrombi and the subsequent embolic phenomena. FRIEDLAND.

Bedford, D. E., Aidaros, S. M., and Girgis, B.: Bilharzial Heart Disease in Egypt. Brit. Heart J. 8:87 (April), 1946.

Cor pulmonale with gross dilatation of the pulmonary artery is by no means rare in Egypt and is usually encountered in young adults suffering from advanced visceral bilharziasis or from severe genito-urinary infection with *Schistosoma hematobium*. A case of "Bilharzial Ayerza's disease" is reported because, in spite of the frequency of this condition in Egypt, the number of cases on record is scanty. The patient, a 34-year-old farmer, was admitted to Kasr-el-Aini Hospital, Cairo, complaining of dyspnea on exertion, productive cough, and precordial pain of three-years' duration. Examination revealed cardiac enlargement but no manifestations of congestive failure other than mild dyspnea. An x-ray film showed great enlargement of the pulmonary artery. Three weeks after admission, he began to have acute congestive failure and died within a few days. Autopsy revealed pulmonary endarteritis due to bilharziasis; atheroma and aneurysmal dilatation of the pulmonary artery and minor branches; hypertrophy and dilatation of the right heart; cirrhosis of the liver; bilharzial splenomegal and bilharzial cystitis.

This disease affects young adults infected with *Schistosoma mansoni* or *S. hematobium* or both. Cyanosis and clubbing of the fingers are relatively slight and clinical and radiological signs of lung disease are slight or absent. Dilatation of the pulmonary artery may amount to aneurysm and relative pulmonary incompetence is common. The x-ray appearance of the heart is similar to that of atrial septal defect. Pathologically, the changes consist mainly of an obliterative pulmonary endarteritis. Histologically bilharzia ova are found in the walls of the small vessels and in extravascular tubercles. In the later stages, the occluded vessels become expanded by highly vascularized tissue to form "angiomas," which are a distinctive feature of bilharzial arteritis.

LAPLACE.

Book Reviews

CLINICAL ROENTGENOLOGY OF THE HEART. By John B. Schwedel, M.D. Annals of Roentgenology, Vol. XVIII, New York, 1946, Paul B. Hoeber, Inc.

In his preface, the author justifies the writing of a new medical book only on the bases of "original contributions or simplicity of presentation or . . . the further development of thesis not fully exploited methods. . . ." In the opinion of the reviewer, he has justified his thesis by fulfilling the second requirement. His descriptive material is clearly presented and is rarely of a controversial character. The very numerous roentgenograms were carefully selected and are of uniformly high technical quality and of sufficient size to make important details easily visible. The diagrams, paired with most of the roentgenograms, are more clearly and quickly explanatory than the usual legends. The addition of a chapter on the lungs in heart disease is welcome and indispensable in a work of this kind. The format of the volume is excellent.

Few adverse criticisms can be offered. It is inevitable that in a first edition of a book with many illustrations some of them will be inverted and others reversed. The book will be chiefly interesting to the roentgenologist and to the cardiologist; the latter would probably prefer more clinical data in the legends, and also more electrocardiograms when these are pertinent and helpful in the diagnosis. This applies particularly to the subject of congenital heart defects, which deserves a somewhat fuller treatment. . . . The valuable contributions of the method of contrast visualization are insufficiently presented. On page 73 appears this statement: "The criterion for left ventricular rounding and enlargement is fulfilled when the arc of the left ventricular segment, if extended, forms a circle, the projected outline of which does not fall beyond the confines of the fluoroscopic screen or the x-ray film. If the circle thus formed is large and extends beyond the fluoroscopic screen, the left ventricle is less likely to be enlarged." (Rule of the circle.) This attempt to draw a relation between the size of the left ventricle and the size of a fluoroscopic screen or x-ray film appears to us to be unscientific. The clinical value of the differentiation of ventricular enlargement into outflow and inflow tract enlargements is not convincingly established. Furthermore, the determination of the lengths of the inflow tracts depends on the accurate localizations, in the left anterior oblique view, of the junction of the left auricular border with that of the left ventricle, and also of the position of the interventricular groove. These localizations are usually difficult, frequently impossible, and almost always uncertain.

Despite these criticisms, the novice and expert, alike, will read this book with considerable pleasure and profit, and it is highly recommended.

A. MARGOLIES, M.D.

NORDISK LAEREBOG I INTERN MEDICIN Vol. IV. Circulatory Diseases. By Erik Warburg, Copenhagen, Gyldenalske, Boghandel, Nordisk Forlag, Copenhagen, 1946, 366 pages.

This volume is part of the standard textbook in internal medicine which is used at the medical schools in Scandinavia. The book is divided into three parts. Part one deals with general aspects of cardiology: pathologic physiology of the cardiovascular system, the mechanism and clinical aspects of myocardial insufficiency, and diagnostic methods. Part two is concerned with the various forms of heart disease; many uncommon conditions are considered. Special sections are given over to the discussion of pregnancy, sport, and surgery in relation to the heart, and to the use of digitalis. The last part, about one-fifth of the book, is devoted to the discussion of diseases of the arteries.

The style is clear, concise, and, of necessity, somewhat didactic, and the book appears readable even to those with but limited knowledge of Scandinavian languages. The author is well oriented in American literature and for its content matter it might well be placed in the hands of American students.

In three respects it is also of interest to advanced students. Its pathophysiologic approach to the field is novel to modern books, though reminiscent of Hirschfelder. It contains many historical references which are not commonly found in American texts: for instance, he refers to Malmsten's diagnosis in vivo of myocardial infarction in 1859 (confirmed by autopsy), to Payne-Cotton's (1869) and Probst's (1882) descriptions of paroxysmal tachycardia, and to Winge and Heiberg's demonstration in 1869 of bacteria in the heart valves which were the site of bacterial endocarditis, and to Jaccond's description of the same disease in 1885. Finally the author has incorporated a great many contributions by Scandinavian workers who have received scant recognition in this country; many of these contributions are theses which contain a great deal of valuable observations. Therefore, the book would be of very great value if it were not for one serious defect: it has no bibliography. While informing the reader of the existence of many valuable contributions, it does not direct him to them. Inasmuch as many of these are theses or are found in Scandinavian publications of limited circulation they may be difficult of access to American readers. It is hoped that this defect may be remedied in future editions.

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THE American Heart Association was founded in 1924 "for the study of and the dissemination and application of knowledge concerning the causes, treatment and prevention of heart disease; the gathering of information on heart disease; the development and application of measures that would prevent heart disease; seeking and provision of occupations suitable for heart disease patients; the promotion of the establishment of special dispensary classes for heart disease patients; the extension of opportunities for adequate care of cardiac convalescents; the promotion of permanent institutional care for such cardiac patients as are hopelessly incapacitated from self-support; and the encouragement and establishment of local associations with similar objects throughout the United States."

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The American Council on Rheumatic Fever, organized in 1944, consists of a group of representatives of all national medical organizations concerned with rheumatic fever. It operates administratively through the American Heart Association and carries out the program of the American Heart Association insofar as that relates to rheumatic fever.

Annual membership in the American Heart Association is \$2.50 and includes twelve issues of *Modern Concepts of Cardiovascular Disease*; Journal membership is \$10.00 and includes a year's subscription to the AMERICAN HEART JOURNAL (January-December), twelve issues of *Modern Concepts of Cardiovascular Disease*, and annual membership in the Association. Contributing membership starts at \$25.00 per year; patron membership is \$50.00 and over per year. Membership blanks will be sent upon request.

The Association earnestly solicits your support and suggestions for its work. Donations will be gratefully received and promptly acknowledged.

Annual Meeting

The Annual Meeting and Twentieth Scientific Sessions of the American Heart Association will be held in Atlantic City, N. J., June 6 and 7, 1947. The Hotel President will be the headquarters for all meetings. On June 6, a meeting will be held with representatives of local Heart Associations to discuss the administrative structure of the American Heart Association with particular reference to program. The annual meeting of members will also be held on that day. The scientific sessions will take place on June 6 and 7. The annual dinner is scheduled for Saturday evening, June 7, at the Hotel President. Meetings begin at 9:00 A.M. each day, and members should plan to arrive on June 5. Hotel rooms will be in great demand and every member who wishes to attend is urged to make reservations immediately.

The chairman of the Program Committee for the Annual Scientific Sessions of the American Heart Association is Dr. Edgar V. Allen, Mayo Clinic, Rochester, Minn. All who desire to present papers at the meetings of June 6 and 7 in Atlantic City should forward to him an abstract of the proposed presentation of not more than 300 words. The deadline for the receipt of abstracts is March 30, 1947.

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Original Communications

OBSERVATIONS ON THE VOLUME OF THE PULMONARY CIRCULATION AND ITS IMPORTANCE IN THE PRODUCTION OF CYANOSIS AND POLYCYTHEMIA

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EVER since the classical studies of Lundsgaard and Van Slyke,¹ pulmonary factors have been recognized to be of great importance in the production of cyanosis. Cournand and Richards,² in a recent report, have analyzed the mechanism of the exchange of oxygen and carbon dioxide in the ventilation of the blood in its passage through the lungs. Little attention, however, has been directed to the volume of blood reaching the lungs for aeration.

The operation developed by Blalock and Taussig³ for the surgical treatment of pulmonary stenosis and atresia offers a unique opportunity to study the effect of increasing the circulation to the lungs in persons suffering from marked reduction in the pulmonary blood flow. The results of the operation demonstrate that, in a person with a congenital malformation of the heart of such a nature as to cause significant reduction in the pulmonary blood flow, both cyanosis and polycythemia are greatly diminished by increasing the circulation to the lungs. Since the importance of the volume of blood flow to the lungs in the production of cyanosis and polycythemia has not heretofore been demonstrated, a brief report on this aspect of the work is warranted.

In our first report,³ Cases 2 and 3 illustrate the extraordinary effect upon the oxygen saturation of the arterial blood which results from an increased pulmonary flow. In Case 2 the oxygen saturation of the arterial blood rose from 36.3 per cent to 73.8 per cent in the first ten days after operation and then gradually rose to 86.7 per cent. During this time the red blood cell count fell from

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7.6 million to 5.7 million and subsequently to 4.9 million. There was a corresponding fall in the hemoglobin and in the hematocrit. The hemoglobin level fell from 24 Gm. to 17.5 Gm. and finally to 15.5 Gm.; the hematocrit reading declined from 78 to 55 and finally to 39. Similar changes were seen in Case 3: during the first three weeks after operation the oxygen saturation of the arterial blood rose from 35.5 per cent to 83.8 per cent and the red blood cell count dropped from 10 million to 6 million; the level of the hemoglobin fell from 26 Gm. to 20 Gm., and the hematocrit from 81 to 54. At the end of the second postoperative month the red blood cell count was 5.5 million, the hemoglobin 13.8 Gm., and the hematocrit 44.

These changes have been repeatedly demonstrated in successive operations. In cases in which the subclavian artery has been used for the anastomosis the degree of improvement has varied with the size of the subclavian artery and the severity of the preoperative condition. In every successful operation in which the innominate artery was used for the anastomosis there has been sufficient increase in the circulation to the lungs to demonstrate clearly the effect of adequate circulation to the lungs. Table I shows the changes in the oxygen content, the oxygen capacity, and the oxygen saturation of the arterial blood, also the red blood cell count, the hemoglobin, and the hematocrit reading in the first twelve cases in which an end-to-side anastomosis between the innominate artery and one of the main branches of the pulmonary artery has been successfully performed and the patients have been followed for at least three months thereafter.

In each instance the operation led to a considerable rise in the oxygen saturation of the arterial blood. In only one instance (Case 5) was there a fall in the oxygen content of the arterial blood. In all the other cases there was a definite rise in the oxygen content of the arterial blood, and in the four cases (Cases 4, 7, 11, and 12) in which the oxygen content of the arterial blood was extremely low there was a marked rise. In every instance in which the oxygen capacity of the arterial blood was abnormally high there was a fall in the oxygen capacity following operation. This fall roughly paralleled the decrease in the hematocrit and in the hemoglobin. These changes occurred more rapidly than did the decline in the red blood cell count. During the ensuing three weeks to one month after operation the oxygen capacity continued to fall and the oxygen saturation to rise, and the red blood cell count, the hemoglobin, and the hematocrit declined. It is a striking fact that it took over a month, usually between two and three months, for the red blood cell count to return to normal.

In Case 7 (that of an infant) there was anemia instead of polycythemia. This infant suffered from an extreme degree of anoxemia. The oxygen content was but 3.01 volumes per cent and the oxygen capacity but 14.6 volumes per cent. The operation caused an increase both in the oxygen content and in the oxygen capacity. The oxygen content rose faster than did the oxygen capacity with the result that there was a definite increase in the oxygen saturation. It is worthy of note that in this instance the oxygen content and the oxygen capacity continued to rise over a period of two months, whereas there was but little increase in the red blood cell count between the second week and the eighth week.

In this series of cases the first postoperative determinations of the oxygen content of the arterial blood were not made until ten days after operation. Nevertheless, the immediate and dramatic improvement in the color of the patient's lips which occurs just as soon as blood is permitted to flow through the new channel to the lungs indicates that these changes begin just as soon as the circulation to the lungs is increased. This clinical impression is substantiated by the few determinations which have been made at the end of the operation after the patient has been breathing air for seven minutes. In one case the oxygen content of the arterial blood rose from 7.5 to 14.5 volumes per cent, the oxygen saturation rose from 30.1 to 69.0 per cent, and the oxygen capacity fell from 25 to 21 volumes per cent. The red blood cell count and the hemoglobin and the hematocrit fell slightly. In another case the oxygen content rose immediately from 6.1 to 18.5 volumes per cent and the oxygen saturation rose from 23.6 to 63.4 per cent.

It is worthy of note that in every instance, although the oxygen saturation of the arterial blood rose significantly, it never reached the normal value of 94 to 97 per cent saturation. This is to be expected because in every instance of tetralogy of Fallot there is some degree of over-riding of the aorta; therefore the aorta always receives some venous blood from the right ventricle. Indeed, the difference between the oxygen saturation of the normal person and the oxygen saturation attained in these cases probably indicates the relative volume of venous blood shunted into the systemic circulation in the presence of adequate circulation to the lungs.

The second significant finding is that even though the oxygen saturation of the arterial blood never reaches the normal value, it appears that in the presence of adequate circulation to the lungs an oxygen saturation of 70 to 88 per cent is sufficiently high to remove the stimulus which leads to the development of compensatory polycythemia. This is shown by the fact that over a period of weeks there is a steady decline in the hemoglobin, the red blood cell count, and the hematocrit, and finally after a period of several months these values have returned to normal.

Additional studies on patients who have come to the Harriet Lane Home for investigation of various cardiac abnormalities have shown that some children with minimal disability may suffer from relatively severe anoxemia. These children have no polycythemia and show slight cyanosis of the nail beds but have lips of normal color. They are able to run and play as other children do. In a group of such children in whom the cyanosis was due to a venous-arterial shunt, the oxygen saturation of the arterial blood was between 66 per cent and 75 per cent. This is exactly what is to be expected on a theoretical basis, for it has long been known that it requires 5 Gm. of reduced hemoglobin in the circulating blood to cause "visible" cyanosis; hence, if there are 15 Gm. of hemoglobin it means that one-third of the blood in the capillaries must be in the reduced form to cause "visible" cyanosis. Nevertheless, it is a striking fact that in young children, if the oxygen saturation of the arterial blood remains above 66 per cent, there is no need for a compensatory polycythemia. This is a far lower level of

TABLE I. THE EFFECTS OF AN ARTIFICIAL DUCTUS ARTERIOSUS ON THE ARTERIAL OXYGEN SATURATION, AND THE RED BLOOD CELL COUNT, HEMOGLOBIN, AND HEMATOCRIT READING OF PATIENTS WITH A TETRALOGY OF FALLOT

CASE	NAME	TIME INTERVAL	ARTERIAL OXYGEN CONTENT (VOLUMES PER CENT)	OXYGEN CAPACITY (VOLUMES PER CENT)	ARTERIAL OXYGEN SATURATION (VOLUMES PER CENT)	RED BLOOD CELL COUNT (MILLIONS)	HEMOGLOBIN (GM.)	HEMATOCRIT READING
1	B. R.	Preoperative	11.7	32.3	36.3	7.5	24	71
		9 days postoperative	20.3	27.5	73.8	6	19	61
		26 days*	19.8	23.9	82.8	6	17.5	55
		5 months	17.6	20.3	86.7	4.9		39.6
2	M. M.	Preoperative	10.7	30.2	35.5	10	26	81
		9 days postoperative	17.7	22.2	79.7	6.2	20	54
		24 days	17.7	21.1	83.8	6	20	53
		2½ months				5.5	13.8	44
3	J. B.	Preoperative	13.3	29	45.9	9.9	20.7	84
		2 weeks postoperative	16.5	22.0	75.6	7.1	17.2	56
		4 weeks	16.6	21.4	77.5	6.2	14	44
		3 months	13.3	17.9	79.3	5.3	13	37
4	J. R.	Preoperative	4.7	22.9	20.5	8.1	22	66
		9 days postoperative	13.3	20.4	65	7.3	16.5	55
		3 weeks	13.1	19.5	67	5.4	14	53
		7 months	15.4	21.1	73	5.2		53
5	J. S.	Preoperative	19.0	28.9	65.8	8.0	23.2	82
		10 days postoperative	18.0	22.6	79.5	6.5	16.5	66
		6 weeks	17	20	85	5.5	14.3	20
		7 months	16.8	20.0	84.0	5.2	17.6	43.6
6	L. S.	Preoperative	11.3	29.3	38.6	9.9		91
		10 days postoperative	12.9	20.1	64.0	6.5		38.2
		6 weeks	Crying 15.7	21.2	74	5.2		52.9
		9 months	Crying 16.0 Quiet	19.4	82.6	4.3		40

*All determinations are postoperative values except the initial ones which are marked preoperative.

TABLE I. THE EFFECTS OF AN ARTIFICIAL DUCTUS ARTERIOSUS ON THE ARTERIAL OXYGEN SATURATION, AND THE RED BLOOD CELL COUNT, HEMOGLOBIN AND HEMATOCRIT READING OF PATIENTS WITH A TETRALOGY OF FALLOT (Cont'd)

CASE	NAME	TIME INTERVAL	ARTERIAL OXYGEN CONTENT (VOLUMES PER CENT)	OXYGEN CAPACITY (VOLUMES PER CENT)	ARTERIAL OXYGEN SATURATION (VOLUMES PER CENT)	RED BLOOD CELL COUNT (MILLIONS)	HEMOGLOBIN (GM.)	HEMATOCRIT READING
7	M. C.	Preoperative	3.01	14.6	20.6	5.7	14	45
		2 weeks postoperative	8.39	17.6	47.7	6	14	42.5
		2 months*	13.8	21.4	64.5	6.2	16.4	53.3
		6 months	Crying 11.6	19.7	58.9	6.3	15.8	48.5
8	J. P.	Preoperative	15.4	31.5	48.9	8.7	24.6	67.7
		2 weeks postoperative	17.0	22.0	77.2	5.9	17.5	54.9
		3 months	16.6	21.5	77.2	5.8	15.2	49.5
9	P. R.	Preoperative	13.7	29	47.2	10.9	23.5	67.8
		10 days postoperative	14.2	21.2	67.0	6.6	15.1	55.6
		3 weeks	14.8	22.8	65	7.3		58.9
		2 months	16.8	23.4	71.5	7.9	19.6	58.3
10	R. W.	Preoperative	16.9	30.7	55.1	9	25.5	82.8
		10 days postoperative	16.2	23.2	69.8	6.4		63
		3 weeks	18.9	25	75.6	7.4	19	68.3
11	P. L.	Preoperative	7.3	25.4	28.7	8.8	20.4	71
		10 days postoperative	14.5	19.3	75.2	6.4	12.8	56.7
		2 weeks	13.6	19.5	69.8	7		54.8
		10 weeks	16.9	21.8	77.6	6.9	15.4	56.8
12	A. B.	Preoperative	7.5	25	30.1	6.4		55.1
		2 weeks postoperative	14.8	17.5	84.1	5.2		41.6
		3 months	13.9 Crying	16.3	85.3	4.6		38.6

oxygen saturation than the normal person can tolerate. The mechanism by which these children are enabled to adjust to this degree of oxygen unsaturation is under investigation.

We do not mean to imply that the lack of circulation to the lungs is the sole cause for the production of cyanosis and polycythemia, or that in the presence of polycythemia all of the blood which passes through the lungs is in effective contact with the oxygen in the alveolae. On the contrary, the change in the patient's color when he is anesthetized and is receiving high concentrations of oxygen, offers clear evidence that without any fundamental alteration in the course of the circulation the oxygen saturation of the arterial blood may be greatly increased. In an attempt to analyze these factors, samples of arterial blood have been obtained prior to operation but after the patient was anesthetized and was receiving oxygen in high concentration. These samples have shown a striking increase in the oxygen saturation due to an increase in the oxygen content of the arterial blood, but, as is to be expected, there was no change in the oxygen capacity. These samples are truly basal, a condition which it is virtually impossible to obtain during an arterial puncture made when a child is conscious. These values are probably influenced both by the inhalation of a high concentration of oxygen and by the basal condition associated with anesthesia, and possibly by the anesthetic agent. The relative importance of these factors is not easy to determine. Nevertheless, the fact that there is a rise in the oxygen saturation of the arterial blood when the patient is given a high concentration of oxygen is in accord with the existence of pulmonary factors emphasized by Lundsgaard and Van Slyke¹ in their classical studies on cyanosis.

Furthermore, we have seen a number of patients in whom there was cyanosis and polycythemia in the presence of adequate or excessive circulation to the lungs. A heart of the Eisenmenger type is an excellent example. The cause of the cyanosis in these patients is by no means clear. In such individuals there may well be some alteration in the pulmonary epithelium or in the pulmonary vascular bed which prevents complete oxygenation of the blood in its passage through the lungs.

It is important to remember that excessive pulmonary circulation places a strain on the heart. This fact has been clearly demonstrated by the benefit derived from the ligation of a large patent ductus arteriosus. Therefore, the desired objective in the surgical treatment of pulmonary stenosis is *adequate*, not excessive, circulation to the lungs. By "adequate" is meant a sufficient volume of blood to remove the stimulus for polycythemia and to raise the oxygen saturation of the arterial blood to the level which permits full or reasonably full activity to the patient without placing an undue strain on the heart. It is hoped that sufficient pulmonary circulation can be established to raise the oxygen saturation of the arterial blood to or above the threshold of "visible" cyanosis and to enable the red blood cell count, the hemoglobin, and the hematocrit to return to and remain within normal limits. Recent experience shows that, in the majority of children, these results can be attained by the anastomosis of the subclavian artery to the pulmonary artery. Furthermore, in many instances,

the anastomosis of the subclavian artery to the pulmonary artery has caused no demonstrable cardiac enlargement. Obviously, if such results can be attained by the use of the smaller vessel, the employment of the subclavian artery is preferable to that of the innominate artery.

CONCLUSIONS

Diminished blood flow to the lungs, such as occurs in the tetralogy of Fallot, causes unsaturation of the arterial blood. When this is extreme and persistent, the condition leads to the development of polycythemia.

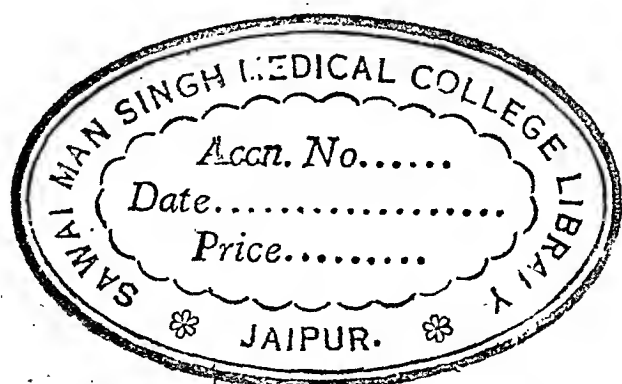
In patients in whom the cyanosis and polycythemia result from lack of adequate circulation to the lungs, increasing the circulation to the lungs increases the oxygen saturation of the arterial blood, lessens the cyanosis, and leads to a reduction in the polycythemia.

An oxygen saturation of 75 to 88 per cent can usually be attained in patients with a tetralogy of Fallot by an anastomosis of the proximal end of the innominate artery to the side of one of the pulmonary arteries. At such a level of oxygen saturation of the arterial blood the stimulus for the production of polycythemia has been withdrawn.

An oxygen saturation of 65 to 70 per cent may be sufficient to enable the child to indulge in unrestricted activity and does not necessarily lead to the development of polycythemia.

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STUDIES ON THE CORONARY CIRCULATION

II. THE COLLATERAL CIRCULATION OF THE NORMAL HUMAN HEART BY CORONARY PERFUSION WITH RADIOACTIVE ERYTHROCYTES AND GLASS SPHERES

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INTRODUCTION

DESPITE the accumulation of considerable material on the coronary circulation during the past 250 years, many questions still remain to be answered. Although it was in 1708 that Thebesius¹ first demonstrated by careful dissection the occurrence of anastomoses between both coronary arteries, the existence of intercoronary arterial anastomoses in normal hearts has been a point of dispute up to the present time. There have been two sharply divergent opinions about this question. First, there are those whose investigations have led to the conclusion that the coronary arteries in normal hearts are end-arteries, and that no anastomoses other than capillaries normally exist. Hyrtl² in 1855, on the basis of injection and corrosion experiments, denied the existence of coronary arterial anastomoses, and in 1866 Henle³ confirmed his work. As the result of their experiments on the clamping of coronary arteries in curarized dogs, Cohnheim and von Schulthess-Rechberg⁴ in 1881 stated that the coronary arteries were end-arteries. More recently, Blumgart, Schlesinger, and Davis⁵ stated that anastomoses larger than 40 micra in diameter are not found in normal hearts, and that these fine intercoronary communications are not of functional significance in obviating the untoward results of rapidly developing coronary narrowing or occlusion. Their method of study, developed by Schlesinger⁶ in 1938, consisted of the injection of a radiopaque lead-agar mass into the coronary arteries followed by unrolling of the heart so that all of the coronary arteries could be visualized in one plane by roentgenography. The filled coronary tree was carefully dissected with the aid of an x-ray of the radiopaque vessels. The lead-agar perfusate regularly penetrated to all vessels 40 micra in diameter, reached about 50 per cent of vessels 20 micra in diameter, and never entered vessels smaller than 10 micra in diameter. When this material was injected into one of the coronary arteries, they were unable to demonstrate its presence in the opposite coronary artery in normal hearts. They therefore concluded that intercoronary anastomoses larger than 40 micra in diameter are not found,

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and that anastomotic communications measuring less than approximately 40 micra in diameter exist between the coronary arteries of normal hearts. However, in pathologic hearts, their conclusions were as follows: "Obstruction to normal coronary arterial blood flow by arteriosclerotic narrowing or occlusion regularly results in the development of intercoronary anastomoses measuring 40 to 200 micra in diameter. Anastomotic circulation develops, then, only when and where it is needed. The development of such anastomoses is not related to age, for they are not present in the hearts of even senile patients when little or no coronary arteriosclerosis is present." Another significant conclusion was that anastomoses over 40 micra in diameter occurred in hypertrophied hearts even in the absence of coronary artery disease.

Employing the same method of study, Ravin and Geever⁷ confirmed the work of Blumgart and co-workers by finding interarterial anastomoses, in the absence of coronary occlusion, in only 21 hearts in a series of 166 hearts studied. In these hearts in which anastomoses were demonstrated, they did not state the condition of the coronary arteries or the size and weight of the heart.

On the other hand, a great body of evidence supporting the existence of intercoronary arterial anastomoses has been accumulated by many investigators, culminating in the classical anatomic studies of Spalteholz and of Gross. Employing methods consisting of the injection of colored or radiopaque gelatin solutions into the coronary arteries, with clearing of the remaining tissues, followed by dissection and roentgenography of the intact heart, Spalteholz⁸ in 1907, and Gross⁹ in 1921, reached the following conclusions: (1) No end-arteries exist in the heart; (2) anastomoses exist between the branches of each coronary artery; (3) anastomoses exist between the right and left coronary arteries both in their capillary as well as precapillary distribution; (4) anastomoses exist between the coronary arteries and vessels from the adjacent and attached organs; (5) anastomoses in the heart are universal and abundant. Furthermore, these observers felt that coronary anastomoses increased with age. Gross emphasized that the development of septal anastomoses and rami telae adiposae (vessels lying in the fatty tissue under the visceral pericardium) begins in the second decade of life and reaches its maximal development in the seventh decade of life.

In 1942, Prinzmetal, Kayland, Margoles, and Tragerman¹⁰ published a quantitative method for determining collateral coronary circulation in human hearts obtained post mortem. Adapting Dock's kerosene perfusion method,^{11,12} they perfused kerosene through both coronary arteries under constant pressure, and the flow through each artery was measured. Then, one of the coronary arteries was suddenly occluded by a clamp just above the cannula, and the flow through the opposite coronary artery was measured. If the flow through the unobstructed vessel increased, then the increase in flow must have necessarily been due to fluid going through the collateral circulation. That is, the increase in the volume of fluid flowing through the unobstructed coronary artery represented that amount of fluid flowing into the vascular tree of the opposite side of the heart distal to the occluded coronary artery, via the available anastomotic channels present. Thus, the percentage of collateral circulation could be meas-

ured. Collateral circulation which averaged 4.16 per cent was found in all but one of twelve normal human hearts. The average collateral flow from the left to the right coronary artery was 19.2 c.c. per minute or 4.55 per cent of the flow through the left coronary artery, while the average flow from the right to the left coronary artery was 6.2 c.c. per minute or 4.05 per cent of the flow through the right coronary artery. It was also found that if a radiopaque gelatin mixture with a viscosity slightly greater than blood was injected into one coronary artery, it regularly appeared at the opposite coronary artery in normal hearts of persons ranging from 3 to 67 years of age. The entire coronary arterial tree was filled as was demonstrated by roentgenography. If this same radiopaque substance was injected into either the anterior descending or the circumflex branch of the left coronary artery, the entire coronary artery tree was also filled.

The fact that the problem of the existence of interarterial anastomoses in the human heart is still unsettled, despite much good work by careful and reliable investigators, has prompted us to seek new methods of study in an effort to cast more light on this controversial subject. A quantitative method for the determination of collateral flow was presented in 1942.¹⁰ In this paper are presented two new methods for the study of the collateral circulation of the heart which help to solve these problems.

STUDIES WITH PERFUSION OF RADIOACTIVE RED CELLS

Human radioactive red cells were perfused through either the anterior descending branch or circumflex branch of the left coronary artery, and the

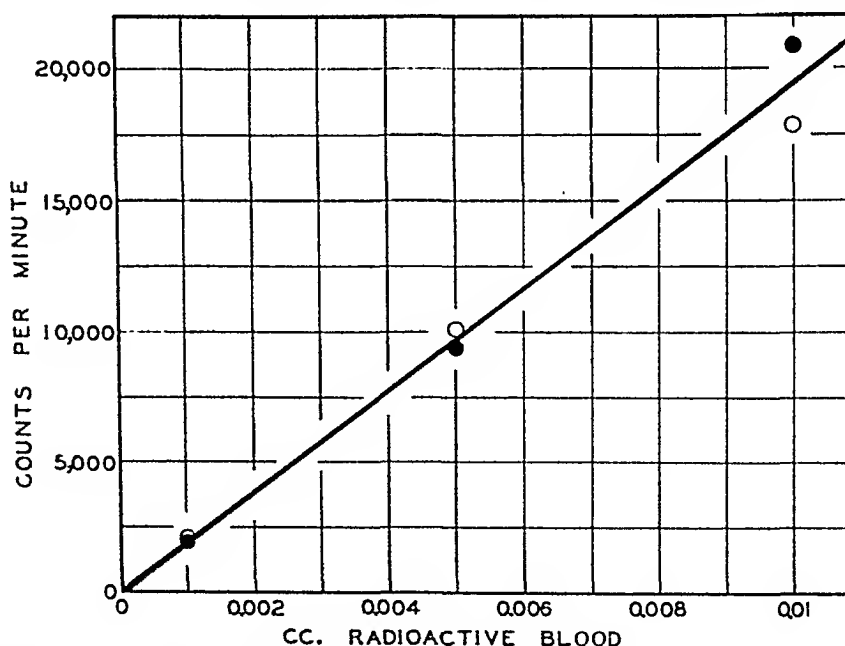


Fig. 1.—Gelger count measurements of various dilutions of radioactive red cells prepared with P32. This red cell suspension was the fluid perfused through the coronary artery in the perfusion experiments. It can be seen that 0.001 c.c. of the red cell suspension was easily measured by the Gelger counter. If larger amounts of radioactive phosphorus are used, it should be possible to detect even smaller volumes of the erythrocyte suspension. The dots and circles represent separate determinations of thin films prepared on glass slides with 0.01 c.c. volumes of erythrocyte suspensions.

distribution and concentration of these erythrocytes were measured in various areas of the ventricular myocardium. This method was utilized because it has the following advantages over the classical techniques for the study of the coronary circulation which involve the injection of radiopaque or colored materials: (1) Since the erythrocytes are labelled, their distribution and concentration throughout the heart can be quantitatively determined; (2) blood is the normal circulatory fluid and is therefore always preferable to other nonphysiologic fluids in studies of the circulatory system; (3) very small amounts of blood containing radioactivity can be measured. This is illustrated in Fig. 1.

Method.—Human hearts were obtained at necropsy, all post-mortem examinations having been performed within twenty-four hours after death. Some hearts were kept in a refrigerator at 4°C. for approximately eighteen hours before the experiment was conducted, and others were perfused immediately following autopsy. Prior to perfusion these hearts were incubated in normal saline solution at 40°C. for one-half to one hour in order to overcome rigor mortis. A glass cannula was then placed and securely tied in either the anterior descending branch or the circumflex branch of the left coronary artery. The right coronary artery and coronary sinus were similarly cannulated. Heavy clamps were applied over the auricles, pulmonary artery, and pulmonary veins in order to prevent leakage from the ventricular cavities and to cut off the circulation to the auricles. Cotton plugs were placed in the pulmonary artery and the aorta at the level of the semilunar valves in order to prevent contamination of the contents of the ventricular cavities from leakage of the perfusate.

Human red blood cells were made radioactive by incubation with radioactive phosphorus (P32 in the form of Na_2HPO_4) as described by Nylin and Malm.¹³ The amount of P32 used for incubation in each experiment varied from 0.5 to 1.0 millicurie per 100 c.c. of a suspension containing equal volumes of erythrocytes and normal saline. The erythrocyte suspension was equilibrated with alveolar air, and incubated at 37°C. for two hours. The red cells were packed down by centrifugation and the supernatant fluid was decanted. Then the red cells were washed with saline two or three times, until the supernatant fluid was practically free of radioactivity. The final composition of the perfusate consisted of equal volumes of labelled red cells and normal saline. If the red cells were packed down by centrifugation at this point it was found that the supernatant fluid had approximately one-eighteenth to one-thirtieth the radioactivity of the cells, depending upon the number of previous washings.

This radioactive erythrocyte-saline fluid was perfused through either the anterior descending branch or the circumflex branch of the left coronary artery at a constant pressure of 100 mm. Hg until the perfusate was seen to issue from the coronary sinus; this usually occurred after only 10 c.c. of blood had been perfused. The total amount of fluid perfused through the heart in each experiment varied from 30 to 90 c.c. and the perfusion was completed in thirty to sixty seconds. The heart was then unrolled in the manner described by Schlesinger,⁶

and the distribution of the radioactive erythrocytes was determined by means of (1) Geiger counts at various arbitrarily chosen sites on the endocardial and pericardial surfaces of the heart, and (2) by exposing the heart to x-ray film for fifteen to forty-eight hours, thereby obtaining a radioautograph. The heart was placed on a sheet of Pliofilm to protect the photographic plate from wetting. The shadow on the exposed plate was produced by the beta rays of the radio-phosphorus in the erythrocytes. The intensity of the shadow was proportional to the amount of blood in all areas and was found to correlate fairly well with the results obtained by the Geiger counts in the corresponding areas (Figs. 3 and 5). In every experiment counts were made on known volumes of the perfusion fluid. One-hundredth of a cubic centimeter of perfusate measured with a micropipette represented the standard used. By calibrating the radioactivity of a known amount of perfusate, the amount of blood in each area could be determined.

All Geiger count measurements of the heart were made under the following conditions. The heart was placed on a lead plate one-fourth inch in thickness.

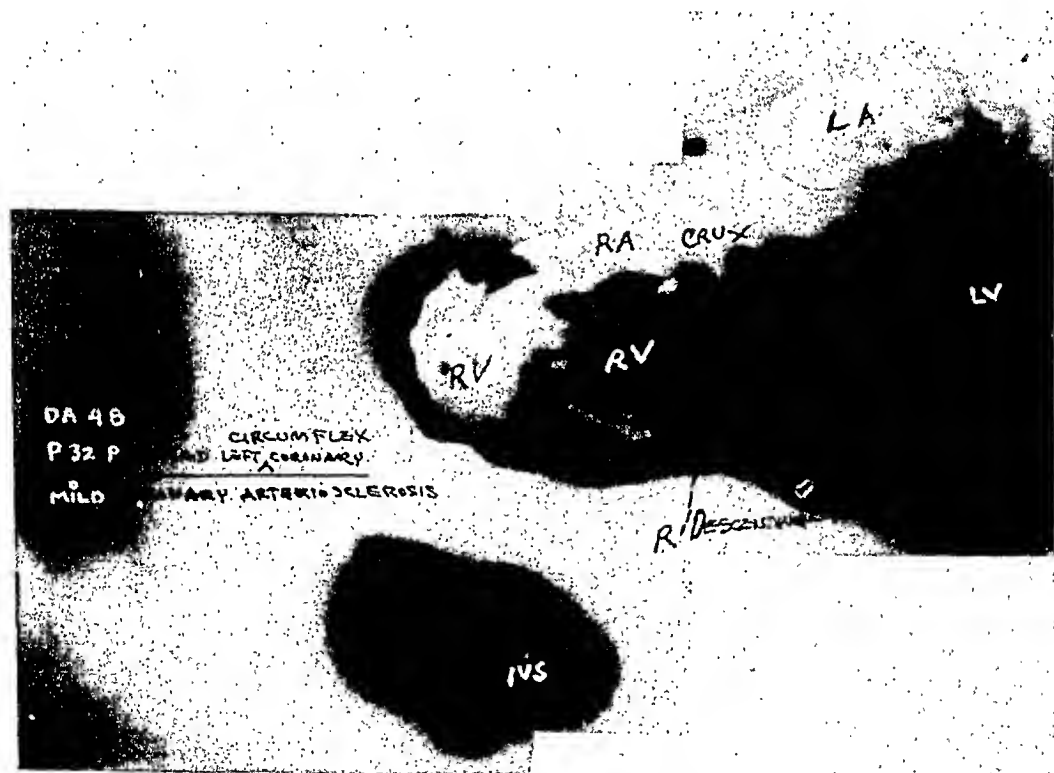


Fig. 2.—Radioautograph. A 62-year-old man died of uremia due to chronic pyelonephritis. Heart exhibits minimal coronary arteriosclerosis. Radioactive erythrocyte suspension was perfused through circumflex branch of left coronary artery. Exposure to x-ray film was twenty-four hours. Heart was unrolled so that all of the coronary arteries lay in one plane. The outlines of the right coronary artery and its posterior descending branch can be seen. The entire left ventricle is well filled with blood. Radioactive erythrocytes are present in all parts of the right ventricle but in lesser amounts than in the left ventricle. The interventricular septum, which was cut out, is well filled with radioactive red cells.

L. A., left auricle; R. A., right auricle; L. V., left ventricle; R. V., right ventricle; I. V. S., interventricular septum; R. Descending, posterior descending branch of right coronary artery.

The area to be measured was placed over a hole in the lead plate which was 1.8 cm. in diameter. The upper surface of the lead plate was 13 mm. above the window of the Geiger counter tube. In this way, the only area that would be measured was that placed over the hole, since the lead plate blocked all beta rays emitted from the rest of the heart. Since beta rays are readily absorbed by tissue, the radioactivity contained in only a 7 mm. depth of tissue was actually measured.

Results.—Perfusion with radioactive red cells was performed on seven normal hearts obtained from patients ranging in age from the newborn infant to 73 years. In all instances the entire left ventricle and septum were well filled with blood. Radioactive red cells were also demonstrated in all parts of the right ventricle, although in lesser concentrations, in every one of these hearts. Radioautographs and measurements of radioactivity expressed in terms of red blood cell equivalents showing these findings are illustrated in Figs. 2 to 6.

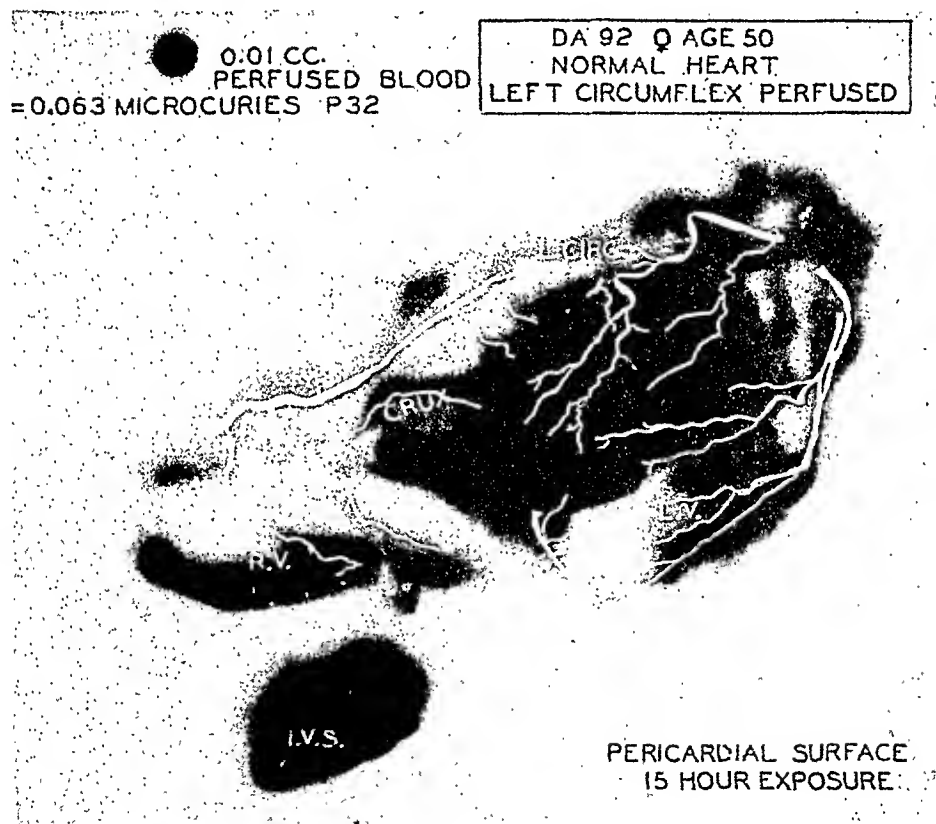


Fig. 3.—Radioautograph. A 50-year-old woman died of bronchogenic carcinoma. Heart normal. Fifty cubic centimeters of radioactive red cells suspension were perfused through the circumflex branch of the left coronary artery at 100 mm. Hg pressure. Perfusion completed in 30 seconds. At completion of perfusion with radioactive erythrocytes, a radiopaque solution was injected into the right and left coronary arteries so that the outlines of the major coronary arteries could be seen by x-ray. The course of these arteries has been superimposed upon the radioautograph for purposes of orientation. Pericardial surface exposed to x-ray film for fifteen hours. The intensity of the shadows in the radioautograph is proportional to the amount of labelled erythrocytes and correlates well with the measurements obtained with the Geiger counter in the corresponding areas.

L. V., left ventricle; R. V., right ventricle; I. V. S., interventricular septum; R. C. right coronary artery; L. Circ., circumflex branch of left coronary artery; L. A. D., anterior descending branch of left coronary artery.

These observations are striking in that they illustrate how abundant amounts of labelled erythrocytes are distributed throughout the entire heart within a matter of a few seconds following perfusion of a comparatively small volume of blood

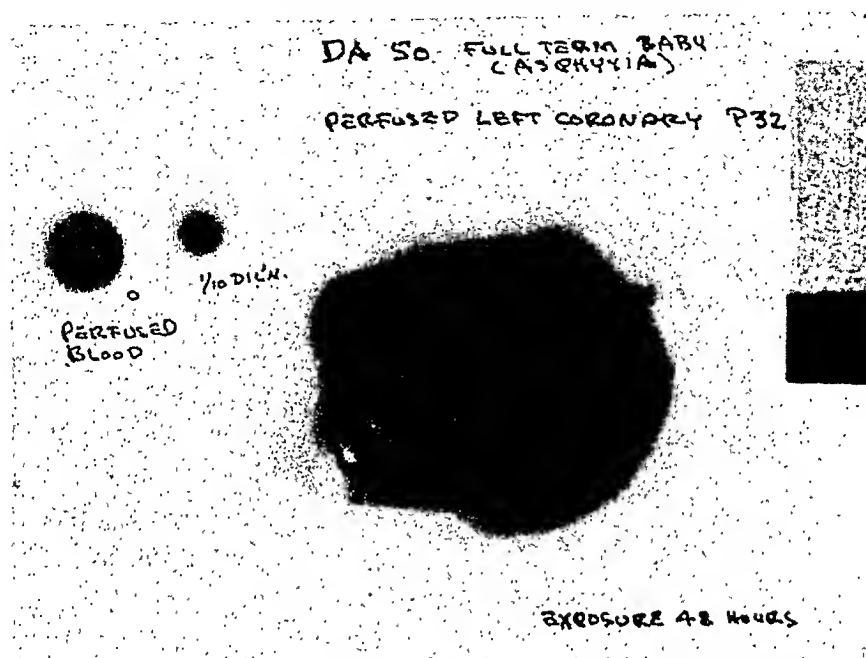


Fig. 4.—Radioautograph of heart of full-term baby who died at birth of asphyxia. Normal heart. Radioactive erythrocyte suspension perfused through left coronary artery. Heart exposed to x-ray film for forty-eight hours. This film was overexposed. However, this film illustrates that the whole heart was well filled with labelled erythrocytes indicating abundant anastomotic channels between the left and right ventricles present at birth.

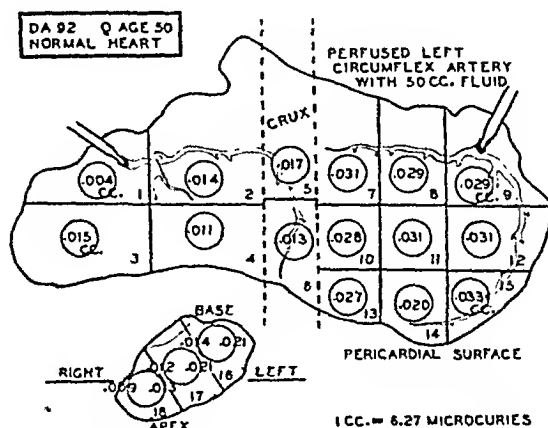


Fig. 5.—Diagram of the volume of radioactive red cells present on the pericardial surface of various areas measured throughout the right and left ventricles. This is the same heart which is shown in Fig. 3 as a radioautograph. Areas numbered 1 to 4 are in right ventricle. Areas 5 and 6 are located at the posterior aspect of the interventricular septum. Areas 7 to 15 are in left ventricle. The course of the right and left coronary arteries are sketched in. Areas 16, 17, and 18 are in the interventricular septum with measurements taken of the right and left surfaces of the septum respectively. The measurements clearly show that the perfused erythrocytes fill the entire left ventricle. They are also present in the right ventricle but in lesser amounts. There were greater amounts of red cells on the left surface of the septum than on the right.

The volumes of erythrocytes recorded are red cell equivalents of radioactivity.

through one of the branches of the left coronary artery. These findings are all the more significant when it is considered that 30 to 50 c.c. of blood is an insufficient volume to fill all the vessels in the heart. Since these red cells can easily pass into any part of the left ventricle, the presence of numerous anastomoses in the left ventricle is indicated. A collateral circulation between the left and right ventricle is demonstrated by the detection of labelled erythrocytes throughout the right ventricle.

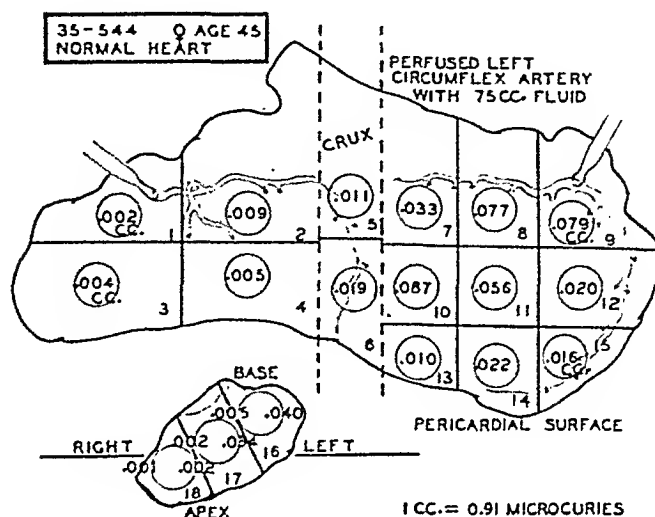


Fig. 6.—Diagram of the volume of radioactive erythrocytes present on the pericardial surface of various areas measured throughout the right and left ventricles. A 45-year-old woman died of carcinoma of the pancreas. Heart normal. Seventy-five cubic centimeters of radioactive red cell suspension were perfused through the circumflex branch of the left coronary artery at 100 mm. Hg pressure. Perfusion completed in 30 seconds. Areas numbered 1 to 4 are in right ventricle. Areas 5 and 6 are located at the posterior aspect of the interventricular septum. Areas 7 to 15 are in left ventricle. The course of the right and left coronary arteries are sketched in. Areas 16, 17, and 18 are in the interventricular septum with measurements taken of the right and left surfaces of the septum respectively. The measurements clearly show that the perfused erythrocytes fill the entire left ventricle. They are also present in the right ventricle but in lesser amounts. There were greater amounts of red cells on the left surface of the septum than on the right.

The volumes of erythrocytes recorded are red cell equivalents of radioactivity.

Perfusion of Glass Spheres

Glass spheres with diameters ranging from 10 to 400 micra were suspended in a radiopaque mixture. This mixture was injected into the cannulated left coronary artery, and the spheres were recovered from the right coronary artery, coronary sinus, and right and left ventricular cavities. The diameters of these recovered beads were determined by microscopic examination with the aid of a calibrated reticule in the eye piece of the microscope. By this means the following facts could be determined: (1) the size of the largest bead recovered from each site of collection, indicating the size of the largest channels allowing the passage of the glass spheres; (2) a percentage distribution graph of the various sizes of beads recovered which could be compared with the percentage distribution of the mixture of beads which was injected. This was determined by measuring the diameters of 200 to 500 spheres.

It follows that after injecting the beads into the left coronary artery, those obtained from the right coronary artery must represent spheres that have tra-

versed channels between the left and right coronary arteries, i.e., arterio-arterial anastomoses. Beads obtained from the coronary sinus represent beads that have traversed channels between the left coronary artery and coronary sinus; i.e., arteriovenous anastomoses. Beads obtained from the right or left ventricular cavities after injection through the left coronary artery represent beads that have come through any or all of the following: arterioluminal vessels, arteriosinusoidal vessels, and Thebesian veins.

Method.—The hearts were obtained and prepared for perfusion in exactly the same way as in the previous experiment. The perfusing fluid consisted of glass spheres* suspended in a radiopaque mixture. Dock's radiopaque mass† was found to be the most suitable medium for suspension of the beads after many experiments with other fluids. Fluids such as kerosene, saline, 6 per cent acacia solution, 20 per cent sucrose, plasma, and blood were found to be unsatisfactory for various reasons. The final composition of the perfusate as used in these experiments was 2 Gm. of glass spheres‡ suspended in 100 c.c. of Dock's radiopaque mass.

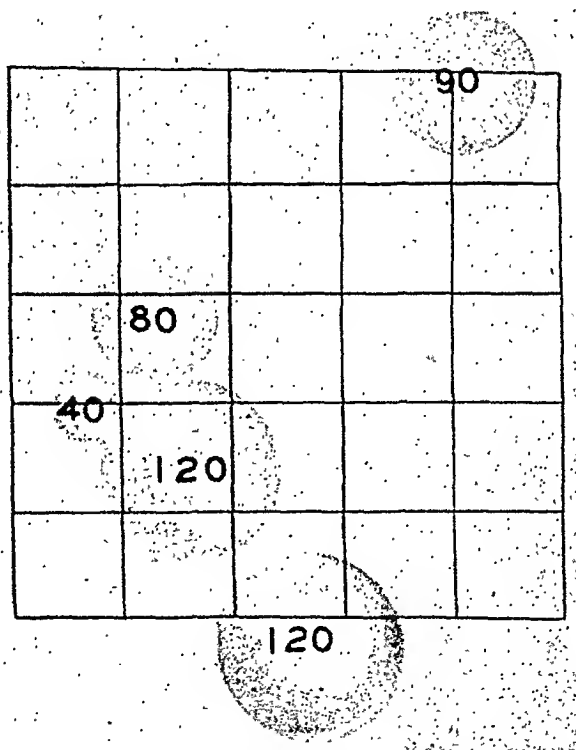


Fig. 7.—Glass spheres as seen under the microscope with reticule superimposed. Each square of reticule is 80 micra under low power. Number superimposed on sphere is diameter of sphere in micra ($\times 100$).

The perfusate was injected into the left coronary artery by means of a 50 c.c. Luer syringe or sometimes an Asepto syringe. The pressure applied was intermittent, but never exceeded 160 mm. Hg and was usually less than this.

*Glass spheres were obtained from Prismo Products, 1211 Architect's Building, Los Angeles, Calif.

†The composition of this mass has been described in detail in a previous publication.¹⁰

‡One gram of beads was estimated to contain approximately 6 million spheres.

Collections of the perfusate containing the beads were then made at the cannulated right coronary artery and at the cannulated coronary sinus. At the completion of the perfusion the fluid present in each ventricular cavity was removed with a pipette after the cotton plugs in the pulmonary artery and aorta were removed.

In order to isolate the glass spheres contained in the radiopaque perfusate, the lead and mercury salts had to be dissolved chemically. First, concentrated sodium hydroxide was added to dissolve the lead carbonate. The supernatant liquid was carefully decanted and the beads were washed with distilled water three or four times. Then small amounts, about 1 c.c. each, of concentrated hydrochloric acid and nitric acid were added, and after gentle heating the mercury sulfide was dissolved. The beads were again washed several times with distilled water. Since the glass spheres are heavier than the washing fluids, they always settled to the bottom of the test tube. The clear supernatant fluid was decanted and the beads at the bottom of the tube were transferred to an ordinary glass slide with the aid of a rubber policeman. Their diameters were determined by microscopic examination with the aid of a calibrated reticule in the eye piece. The appearance of the spheres is shown in Fig. 7.

Results.—

Right Coronary Artery: Glass spheres were injected into the left coronary arteries of thirteen hearts with normal or minimally arteriosclerotic coronary arteries, obtained from patients ranging from 4 to 73 years of age. Arteries were considered to be minimally arteriosclerotic if a few flat yellowish plaques without calcification or encroachment upon the arterial lumen were present in one or more of the major coronary arteries or its branches. This was determined by careful anatomic dissection. These hearts were not hypertrophied, and none of these were obtained from patients who had clinical evidence of heart disease during life. As can be seen in Table I, glass spheres were recovered from the right coronary artery in all but two instances. In these eleven hearts, the largest spheres recovered ranged in size from 70 to 180 micra in diameter. In eight of these eleven hearts, the maximum size of the beads was 70 to 90 micra in diameter. It must be concluded that in eleven of the thirteen normal hearts measured, channels of arteriolar dimensions were present between the right and left coronary arteries. In this small series no variations with age were apparent. In a few hearts tested with either severe coronary arteriosclerosis and/or definite ventricular hypertrophy the maximum size of the beads recovered from the right coronary artery ranged from 120 to 150 micra in diameter (Table I).

Coronary Sinus: The findings with reference to spheres recovered from the coronary sinus were of interest. In all but one of the thirteen normal hearts beads were recovered from the coronary sinus following injection into either the left or right coronary artery. The maximum diameter of the spheres recovered ranged from 70 to 170 micra. In seven of thirteen instances the maximum size was greater than 100 micra. It is quite obvious that channels of larger magnitude than capillaries must exist between the coronary arteries and coronary veins to allow the passage of spheres of such dimensions. Therefore, the presence

TABLE I

NO.	DIAMETERS OF PERFUSED HEADS (MICRA)	AGE	SEX	CAUSE OF DEATH	LARGEST DIAMETERS OF RECOVERED HEADS (MICRA)			
					RIGHT CORONARY	CORONARY SINUS	RIGHT VENTRICLE	LEFT VENTRICLE

<i>Normal or Minimal Coronary Arteriosclerosis</i>								
1	10 to 240	4	M	Sarcoma of leg	80	130	90	170
2	10 to 240	23	F	Postoperative anuric uremia	160	80	190	150
3	10 to 240	27	F	Chronic ulcerative colitis	70	110	—*	—*
4	10 to 440	30	F	Thrombocytopenic purpura	80	70	70	220
5	10 to 440	38	M	Acute appendicitis with perforation	90	90	180	170
6	10 to 240	40	M	Bronchogenic carcinoma	70	160	150	80
7	10 to 240	41	M	Far advanced pulmonary tuberculosis	—†	140	100	100
8	10 to 440	45	F	Hepatic carcinoma	170	80	90	170
9	10 to 240	60	F	Carcinoma of cecum, pulmonary embolism	70	170	200	170
10	10 to 440	65	F	Cirrhosis of liver	180	—†	—*	—*
11	10 to 240	67	M	Carcinoma of stomach	70	90	170	200
12	10 to 240	67	M	Malignant lymphoma Hodgkin's type	80	160	180	200
13	10 to 240	73	M	Carcinoma of cecum	—†	150	160	200

<i>Moderate to Severe Coronary Arteriosclerosis</i>								
1	10 to 240	62	M	Acute posterior wall myocardial infarction*	130	170	120	180
2	10 to 240	63	F	Carcinoma of sigmoid	150	170	160	160
3	10 to 240	65	F	Arteriosclerotic heart disease, congestive failure	—†	80	160	160
4	10 to 440	72	M	Carcinoma of esophagus	150	300	140	180

<i>Ventricular Hypertrophy</i>								
1	10 to 440	39	M	Malignant hypertension with uremia	150	140	300	110
2	10 to 440	64	M	Multiple myeloma	120	160	160	230
3	10 to 440	68	M	Rupture of abdominal aortic aneurysm	• 120	200	120	190
4	10 to 440	70	M	Chronic emphysema, cor pulmonale	130	360	80	350

*None collected in this experiment.

†No heads came through.

‡Left coronary artery torn. Injected through right coronary artery.

of arteriovenous anastomoses in the human heart may be inferred. In the few pathologic hearts studied, the greatest diameters of beads obtained from the coronary sinus ranged from 80 to 360 micra.

Right and Left Ventricles: The maximum sizes of beads recovered from the ventricles ranged from 70 to 350 micra in diameter in both normal and pathologic hearts. Since the beads were injected into the left coronary artery they reached the ventricular cavities via three possible routes: arterioluminal vessels, arteriosinusoidal vessels, and Thebesian veins. No apparent difference was noted between the right and left ventricles.

Percentage Distribution Graph: Graphs illustrating the percentage distribution of beads recovered from each collecting site are illustrated in Figs. 8 to 10.

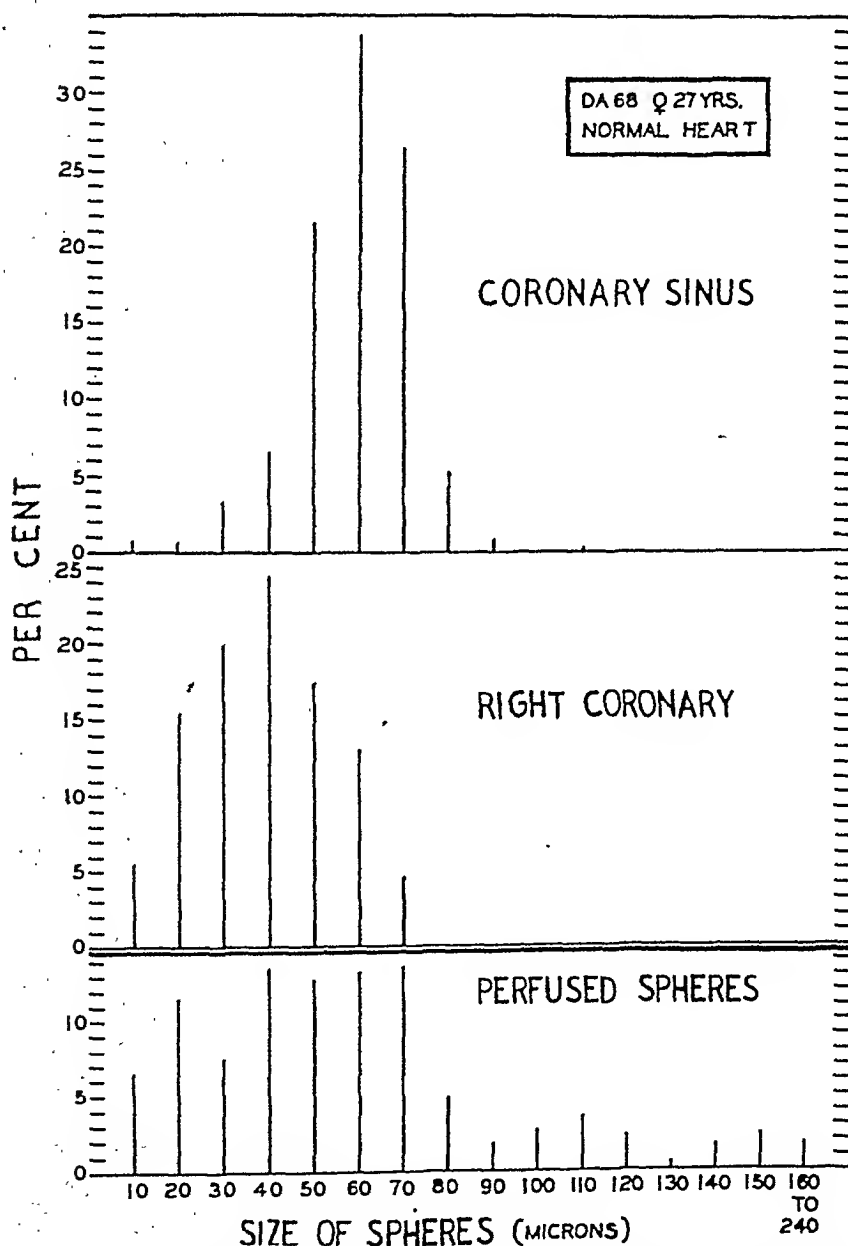


Fig. 8.— Graph showing percentage distribution of glass spheres. A 27-year-old woman died of chronic ulcerative colitis. Normal heart. One hundred and fifty cubic centimeters of radiopaque solution containing glass spheres were injected into the left coronary artery, and spheres were recovered from coronary sinus and right coronary artery. Percentage distribution of beads recovered from coronary sinus and right coronary artery compared with distribution of spheres which were perfused. In this experiment no attempt was made to collect beads from the ventricular cavities.

The number of beads of each diameter is expressed as the percentage of beads of each size in relation to the total number of spheres counted. These graphs show the diameter of the largest sphere recovered and the percentage of spheres of various sizes recovered. These do *not* show the percentage of anastomotic channels of any given diameter because many of the smaller beads may traverse larger channels. At the same time many small channels may be blocked by larger beads in the heart.

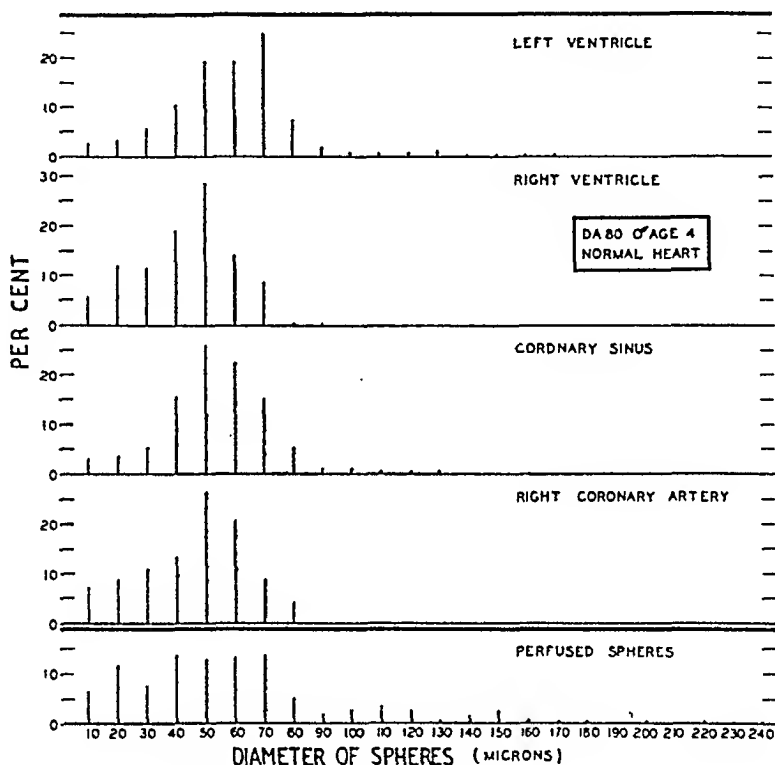


Fig. 9.—Graph showing percentage distribution of glass spheres. A 4-year-old boy died of sarcoma of the leg. Normal heart. Radiopaque solution containing glass spheres was injected into left coronary artery, and spheres were recovered from right coronary artery, coronary sinus, and right and left ventricular cavities. Relatively large anastomotic channels are present in the heart of a young individual.

When this work was begun it was thought that by knowing the percentage distribution and weight of the glass spheres injected and of those recovered it would be possible to calculate the number of anastomotic channels of various diameters present in the heart between any two points, as, for example, the number of channels of 50 micra in diameter existing between the right and left coronary arteries. Mathematically this was possible and Dr. Ernst Snapper of Los Angeles has worked out the following formula for this purpose.

Supposing a bead of size i micra to be present in the fluid recovered after perfusion of the vessels, one may assume that the number of beads of size i micra is proportional to the weighed sum of the vessels through which the beads may pass. Each vessel is weighted by the square of its minimum diameter.

If N_i = number of vessels of diameter i micra

T_i^{i+10} ; T_{i+10}^{i+20} = number of vessels whose minimum diameter ranges from $i+10$ to $i+20$ to $i+10$, where $i+10 > i$; $i+20 > i+10$

N_i ; N_j ; N_k = per cent of beads of size i ; j ; k micra in the fluid injected.

P_i ; P_j ; P_k = per cent of beads of size i ; j ; k micra in the fluid recovered.

$$\text{Then } N_i = \frac{T_{i+10}^{i+20}}{T_i^{i+10}} = \left[\frac{\frac{N_k}{N_j} - \frac{P_k}{P_j}}{\frac{P_i}{P_j} - \frac{N_i}{N_j}} \right] \left(\frac{N_i}{N_k} \right) \left(\frac{i+5}{i+15} \right)^2$$

Vessels of size up to k micra play a role only if $\frac{P_j}{P_k} > \frac{N_j}{N_k}$ and the denominator of the principal formula is positive.

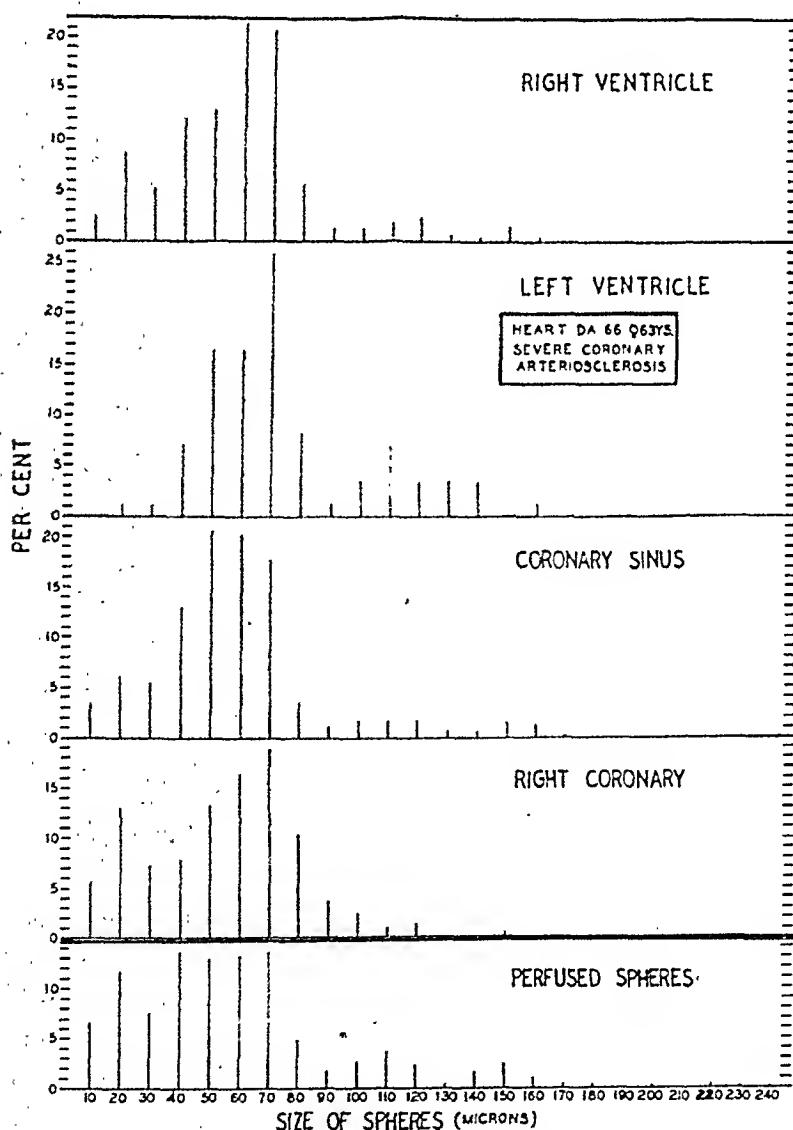


Fig. 10.—Graph showing percentage distribution of glass spheres. A 63-year-old woman died of carcinoma of sigmoid colon. Severe coronary arteriosclerosis. One hundred twenty cubic centimeters of radiopaque solution containing glass spheres were injected into left coronary artery, and spheres were recovered from the right coronary artery, coronary sinus, and right and left ventricular cavities.

We have spent a great deal of effort trying to apply this formula to our experiments. However, it was found that settling of the spheres within the heart during perfusion always occurred. Since this settling factor is obviously an inconstant one, varying not only from heart to heart but also in different vessels in the same heart, this formula could not be applied to the work herein reported. Consequently only the largest-sized anastomotic channels could be determined by the present method.

DISCUSSION

Methods of Study.—Because of the difference of opinion in the literature concerning the existence of intercoronary anastomoses it was felt that a reinvestigation of the problem employing new means of approach might be fruitful, hence the introduction of the two methods of study presented in this paper.

The use of radioactive red cells as a perfusion fluid in post-mortem studies of the heart has several advantages over other perfusion media which have been used in the past, as has already been pointed out. It has been shown that the gross estimation of collateral circulation in the post-mortem heart by older methods does not approach the sensitivity achieved by the use of radioactive red cells. Therefore, these older procedures give an incomplete picture of the extent of the collateral circulation. The abundance of collateral channels present in the normal heart has not been fully appreciated. The sensitivity of labelled erythrocytes suggests its application for other studies, such as the blood supply of the normal heart valve, a much disputed problem. Nylin^{13,14,15} has published some interesting studies in which radioactive blood was injected intravenously in the living patient. In this way he has been able to determine the blood volume.

One of the major deficiencies in the use of dyes and radiopaque solutions for demonstrations of the coronary circulatory bed has been that no strictly quantitative determination of the diameters of the collateral vessels has been achieved. The use of perfusates with varying viscosities and composition has resulted in varying degrees of filling of the coronary tree and its collateral channels. For example, if watery solutions or gelatin-sucrose mixtures with a viscosity slightly greater than blood are perfused through one of the coronary arteries of a normal human heart, they are seen to issue from the opposite coronary artery within a few seconds; if a lead-agar mixture with a viscosity three times greater than that of blood is so perfused, it cannot be detected by x-ray in any part of the circulatory bed of the opposite coronary artery, although the entire tree of the perfused coronary artery is well filled. Obviously, these differences are inherent in the physical properties of each of the perfusates employed. Therefore, it is difficult to accept completely any quantitative criteria as to the smallest diameters of channels through which these fluids will pass. For these reasons it was decided to perfuse glass spheres of graded size through the coronary arteries of the normal human heart. By this means one could unequivocally determine the largest diameters of collateral channels that would permit passage of the spheres. The objection may be raised that the beads were forced through these communicating vessels by the effect of the applied perfusing pressure resulting in stretching of

the lumen of the vessels. Because physiologic perfusion pressures were employed, we do not believe that this objection is a valid one. It is freely admitted, however, that measurements of the lumina of vessels in the post-mortem heart may not necessarily correspond to the actual measurements of the diameters of these vessels in life, because after death neurohumoral influences are absent; nevertheless, the post-mortem measurements are indicative of the maximum diameters these lumina are capable of attaining under appropriate circumstances.

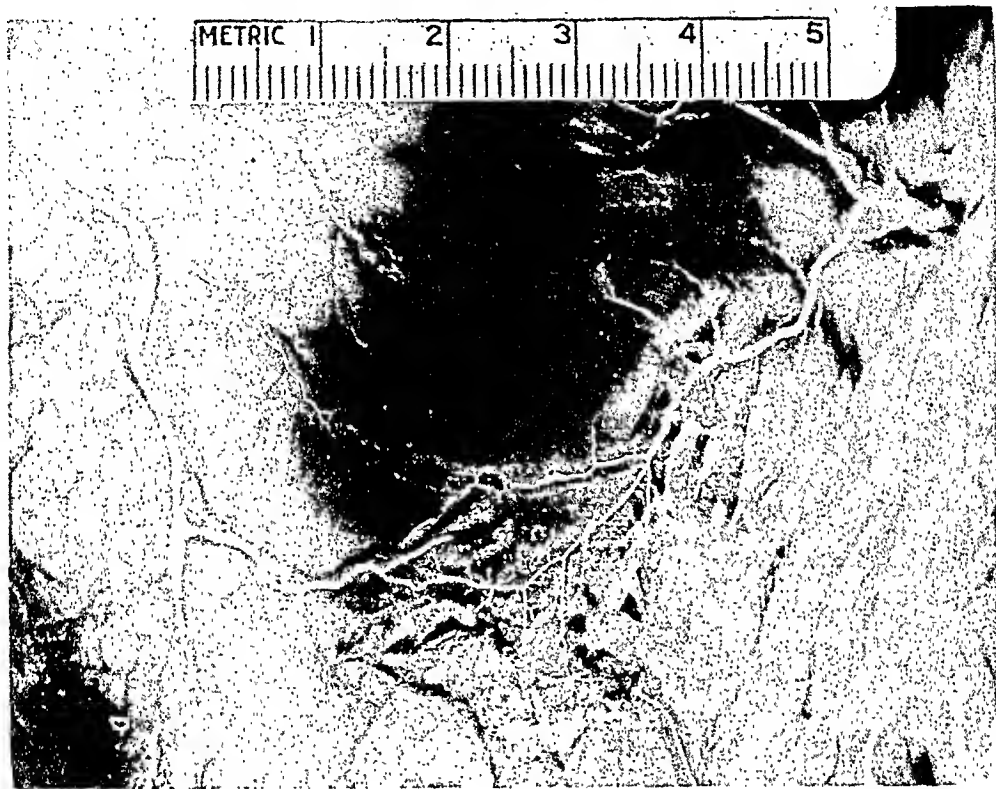
The perfusion of glass spheres of known diameters can be utilized for the study of the circulation of other organs such as the kidney, the lung, and the extremities. At present we are investigating the circulation of the kidney by this method. We had hoped to determine quantitatively the number of anastomoses of various sizes in the heart. This was mathematically possible, but because of settling of the beads within the vessels of the heart, the calculations could not be adapted to the conditions of the experiment. However, with variations in the technique this may still be possible. Possibly a perfusing fluid which will suspend the beads more evenly without settling can be found. The size of the spheres injected can be varied as desired.

In some preliminary observations,¹⁶ living rabbits were given intravenous injections of small amounts of glass spheres without any apparent ill effects, whereas a single, large, intravenous dose resulted in convulsions and death. A few rabbits received repeated small intravenous doses over a period of two or three months without any obvious harm. When these animals were killed, the lungs were found to be packed with beads, and right ventricular hypertrophy was observed. No beads were found in any of the other viscera. It was inferred from these experiments that compensatory anastomotic channels had developed in the lungs of these animals in order for them to survive, because the total dose of beads administered to these rabbits greatly exceeded the minimal lethal dose.

Arterio-Arterial Anastomoses.—In the past several years most investigators have agreed that there are communicating vessels between the coronary arteries in the normal human heart but there has been no concurrence of opinion regarding their size. The present studies quantitatively measured the largest diameters of the intercoronary vessels. These channels were found to have diameters ranging from 70 to 180 micra; these diameters fall within the dimensions of arterioles. As defined by Maximow and Bloom¹⁷ the caliber of capillaries in man averages 8 micra, whereas "the smallest arteries, 0.3 mm. in diameter or smaller are usually grouped in a separate class and are called *arterioles*." According to these definitions, our studies indicate that there are arteriolar anastomoses between the coronary arteries in the normal human heart. Dr. Clara Margoles in this laboratory has demonstrated grossly such an interarterial anastomosis in a normal heart of a 40-year-old man. By dissection this vessel was found to connect the marginal branch of the right coronary artery and the anterior descending branch of the left coronary artery. It is easy to see how relatively large spheres can pass through a vessel of such size (Fig. 11, A, B, and C).

In our small series of normal hearts, the diameters of the intercoronary connections did not appear to increase with age. This was also true with respect

to kerosene collateral flow measurements in normal hearts previously reported from this laboratory.¹⁰ Blumgart, Schlesinger, and Davis⁵ found no differences with increasing age in their study of normal hearts with the lead-agar perfusion method. These findings do not support the work of Gross⁹ and Spalteholz⁸ who found increasing anastomoses with increasing age.



A.

Fig. 11.—Gross anatomic demonstration of an interarterial anastomosis. The coronary arteries are filled with radiopaque gelatin solution which had been perfused through both coronary arteries. A, Demonstration of an anastomosis between the marginal branch of the right coronary artery and the anterior descending branch of the left coronary artery in situ.

B, Demonstration of the same interarterial anastomosis after the coronary arteries were dissected away from the heart.

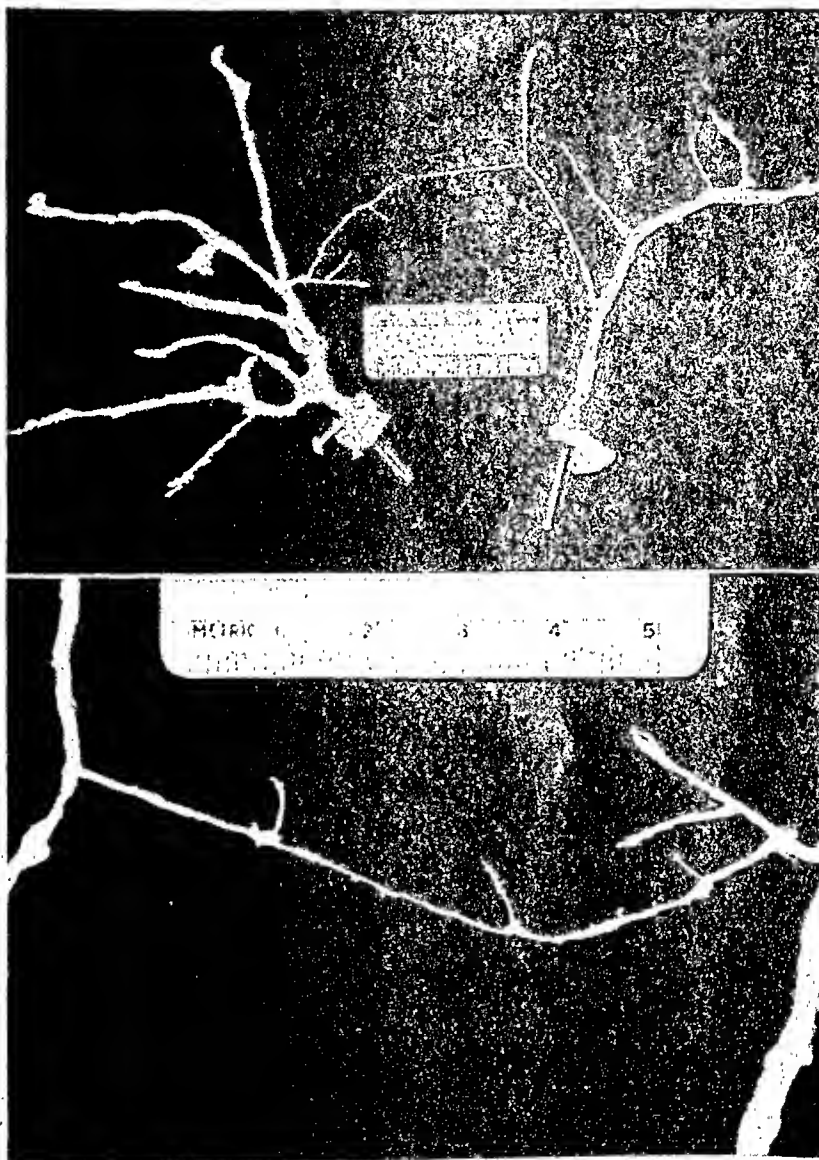
C, Magnification of B, illustrating that the gross diameter of the anastomosis was approximately 0.5 mm. This anastomosis is of arteriolar dimensions.

That intercoronary anastomoses increase in size in the presence of coronary arteriosclerosis or cardiac hypertrophy has been demonstrated by the work of Blumgart and associates and others. In a few such pathologic hearts our findings are entirely in agreement with their observations.

Arteriovenous Anastomoses.—The question of arteriovenous anastomoses in the human heart has apparently been neglected in the past. There are very few references pertaining to this important subject in the literature. In 1911, Nussbaum¹⁸ described direct connections between arteries and veins, made up of a single layer of endothelium, possessing no muscular coat, and lying in the subendocardium. He considered these as safety outlets for arterial blood when the pressure becomes too high. Wearn¹⁹ has stated the following: "Arteriolar-

venous communications also occur in normal hearts. They are infrequently found during a study of serial sections of the myocardium. Because of their rarity, they are probably of little importance." Hirsch²⁰ described vascular segments in the human heart histologically similar to vessels found in the glomus bodies of the digits; these glomus structures were arteriovenous anastomoses. He thought that these intracardiac glomus bodies functioned as "regulators between the internal arterial pressure and the interstitial pressure of the cardiac musculature acting upon the wall of the vessels."

B.



C.

Fig. 11 (Cont'd).—For complete legend, see opposite page.

In the present studies, relatively large glass spheres have been regularly obtained from the coronary sinus following injection into the right or left coronary artery. It is quite obvious that channels of larger magnitude than capillaries must exist between the coronary arteries and coronary veins to allow the passage of these spheres. The regular occurrence of such arteriovenous anastomoses in all hearts studied raises the question of the possible functional significance of such communications. The question is posed whether or not they

supply a mechanism to increase blood flow and provide more efficient regulation of the myocardial circulation analogous to the glomus bodies in the extremities. It is not inconceivable that such channels could allow arterial blood to supply the myocardium by (1) direct supply to the capillary bed, and (2) a shunt into the coronary veins which are connected with Thebesian vessels and capillaries. Thus, it is theoretically possible for ventricular muscle to get oxygenated blood through arteriovenous anastomoses even if a coronary artery is occluded. Unlike intercoronary anastomoses, these arteriovenous shunts should be able to function in a normal heart since the venous pressure is always less than the arterial pressure.

Functional Significance of the Collateral Circulation.—All of the investigations on the collateral circulation of the heart done in this laboratory during the past five years confirm the opinion of those who believe that there are extensive collateral channels of various types in the normal human heart. Most of this work has been of an anatomic nature and has not served to elucidate experimentally the physiologic significance of these vessels during life. It can only be stated teleologically that since these anastomotic communications have been demonstrated they must serve some useful function, although at present their physiologic significance is poorly understood.

Wiggers²¹ has emphasized that, although intracardiac anastomoses have been anatomically demonstrated, the coronary arteries are physiologically end-arteries. With sound logic he has pointed out that the absence of pressure gradients between the coronary arteries precludes the functioning of intercoronary anastomoses in the normal heart. Although this is probably true in the case of interarterial anastomoses in the normal heart, this would not be true in regard to arteriovenous anastomoses because of the presence of an arteriovenous pressure gradient, as we have pointed out.

When one of the coronary arteries is gradually occluded, the arterial pressure distal to the narrowing or occlusion diminishes, and thus establishes a pressure gradient which now allows blood to flow from the opposite coronary artery through the existent anastomotic channels. In this way a functioning collateral circulation develops, by the enlargement of the anastomotic channels which have been shown to be present in this study. In the instance of a slowly developing coronary occlusion, this concept is not disputed and serves to explain the development of a functioning collateral circulation which has been well-demonstrated by radiopaque injection techniques and retrograde flow studies.

In this regard two other possibilities present themselves. If gradual occlusion or narrowing occurs simultaneously in both coronary arteries, there would be no pressure gradient and the function of the anastomotic channels between these arteries would therefore be limited following an occlusion of one of the coronary arteries. Another possible factor which would limit the functional capacity of intercoronary anastomoses would be the occurrence of arteriosclerosis of these channels with resulting narrowing or occlusion. Since these vessels are of arteriolar dimensions, there is no reason why arteriosclerosis can-

not occur in these locations just as in other arterioles throughout the body. We do not believe that this possibility has been heretofore appreciated, and therefore deserves further study.

When one of the coronary arteries is acutely occluded in an otherwise normal heart, are the collateral channels, which are anatomically known to exist in the normal heart, functionless? There is evidence to show that these anastomoses do function, although in a limited way. It is well known that the infarcted area in normal hearts is smaller than that supplied by the obliterated vessel. This has been demonstrated in man^{22,23} and in experimental work on dogs.²⁴ Therefore, the rim of viable tissue around the infarct must be supplied by collateral vessels from other arteries. If a small enough artery is obstructed, collateral circulation might be sufficient to prevent myocardial necrosis.

In a previous communication¹⁰ it was shown that if one coronary artery was suddenly occluded in a normal heart, an increase in flow in the opposite coronary artery resulted. This increase in flow was interpreted as representing the degree of collateral circulation present in the heart. Although these experiments were performed on post-mortem human hearts in which all neurohumoral influences were absent, they demonstrated the fact that collateral channels were present ready to function immediately when the need arose. There is evidence^{25,26} to show that concomitant with a coronary arterial occlusion, vasoconstriction may occur in the uninvolved coronary arteries. Sectioning the stellate ganglia²⁷ and upper five thoracic ganglia²⁶ prevented a reduction in coronary flow following ligation of one of the coronary arteries. This may explain why retrograde flow is so small following coronary arterial ligation. This factor, therefore, may greatly limit the possible function of collateral channels immediately following an acute occlusion.

Eckstein, Gregg, and Pritchard²⁸ measured retrograde flow distal to the ligation of the descending branch of the dog's left coronary artery. Immediately following coronary occlusion the retrograde flow was nearly constant at values between 0.5 to 5.8 c.c. per minute, and then it increased very slowly after some hours to reach sizable values in a week or so. For example, the retrograde flow increased from 3.4 to 6.8 c.c. per minute within forty-eight hours, and to 18 c.c. per minute within a week. They also observed that the "retrograde flow from the acutely occluded left descending artery decreased markedly following occlusion of the circumflex artery. After the circumflex artery was again released, the retrograde flow increased in spite of a further fall in blood pressure. Similarly the retrograde flow from the chronically occluded circumflex artery decreased by 33 per cent following occlusion of the left descendens artery." All of these observations indicate that the collateral circulation does function following an acute coronary occlusion. It does not appear likely that the increase of retrograde flow in a matter of hours can be attributed to the formation of new collateral channels, but rather to the utilization of an already existent collateral circulation.

In view of all the evidence cited, our conception of the collateral circulation of the normal human heart may briefly be stated. There are numerous anasto-

TABLE II

SPHERES COLLECTED FROM	DIAMETER (MICRA)	ANASTOMOSIS
Right coronary artery	70 to 180	Arterio-arterial
Coronary sinus	70 to 170	Arteriovenous
Right ventricular cavity	70 to 200	Arterio-luminal vessels Arterio-sinusoidal vessels Thebesian veins
Left ventricular cavity	80 to 220	

motoc channels of various types in the normal heart as has been demonstrated by anatomic studies. These have been diagrammatically summarized in Fig. 12. A summary of the diameters of the various collateral channels in the normal human heart as determined by these experiments is shown in Table II. We wish to emphasize the existence of arteriovenous anastomoses which have received little attention in the past and which deserve further study. All anastomotic channels are ready to function immediately when the need arises. The collateral circulation of the heart is not as adequate as the collateral circulation of such vessels as the femoral or carotid arteries following acute occlusion.²⁸ The degree of collateral circulation in the heart is not sufficient to prevent an infarct following obstruction of a major coronary artery but may limit the size of the infarction. Following acute coronary occlusion the intracardiac collateral circulation functions but in a limited way. With the passage of time, the available anastomoses enlarge.

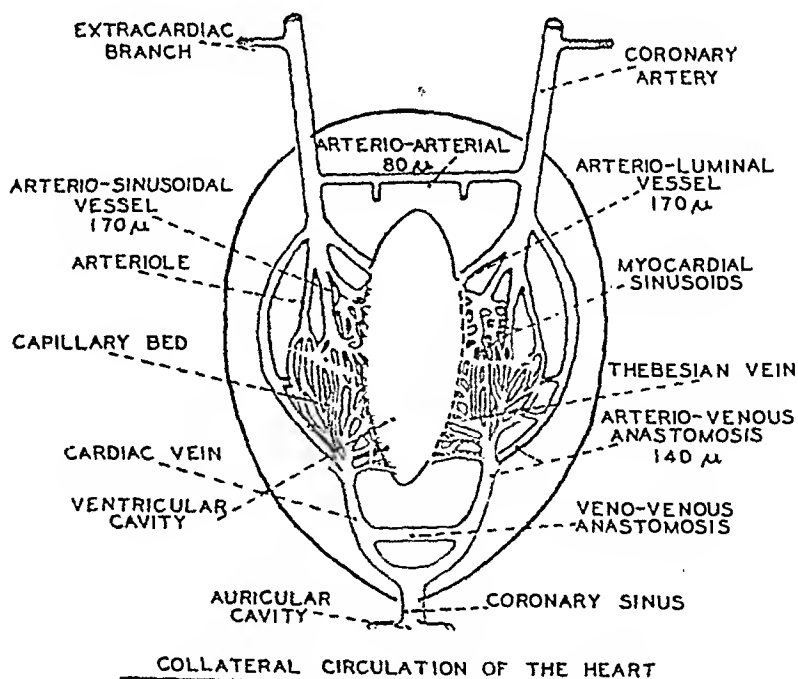


Fig. 12.—Diagrammatic representation of the collateral circulation of the normal human heart. All of these various collateral channels have been demonstrated anatomically.

SUMMARY AND CONCLUSIONS

1. Two new methods for the study of the collateral circulation of the post-mortem human heart have been presented in order to gain further information about this circulation in the normal heart.

2. The first method utilizes a saline suspension of erythrocytes labelled with radioactive phosphorus as a perfusion medium which can be detected and measured quantitatively in any area of the heart. This method has been demonstrated to be very sensitive in that very small quantities of radioactive red cells can easily be measured. Since blood is the normal circulatory fluid, it is preferable to other nonphysiologic fluids in studies of the circulatory system.

3. After perfusion of radioactive red cells through one of the branches of the left coronary artery in normal hearts, abundant amounts of the labelled erythrocytes were found throughout the left and right ventricles. These findings indicated the existence of numerous anastomoses in the left ventricle and of a collateral circulation between the right and left ventricles in the normal post-mortem human heart.

4. The second method of study consisted of the injection of glass spheres of known size through one of the coronary arteries of the post-mortem human heart. The spheres were collected at the opposite coronary artery, the coronary sinus, and the ventricular cavities. In this way the diameters of the various anastomotic channels in the normal human heart could be quantitatively measured.

5. The largest intercoronary arterial anastomoses in the normal human heart allowed the passage of spheres ranging from 70 to 180 micra in diameter. These facts demonstrated that there are intercoronary anastomoses of arteriolar dimensions in the normal heart.

6. The existence of arteriovenous anastomoses was indicated by the recovery of glass spheres 70 to 170 micra in diameter from the coronary sinus following injection of the spheres into the left or right coronary arteries. Very little attention has been focused upon these channels in the past, and nothing is known of their functional significance in the heart. They may serve as a source of oxygenated blood to the myocardium following a coronary arterial occlusion.

7. The diameters of the anastomotic channels between the coronary arteries and either of the ventricular cavities range from 70 to 220 micra. These channels represent one or all of the following vessels: arterioluminal, arteriosinusoidal, and Thebesian veins. No apparent difference between the right and left ventricles was noted with respect to the size of these communications.

8. The normal human heart has an extensive collateral circulation with anastomotic channels of various types. When the need arises, this collateral circulation is ready to function immediately at which time the anastomotic communications may become enlarged in the presence of a favorable pressure gradient. There is evidence to show that the collateral circulation does function following an acute coronary occlusion, but only in a limited manner.

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INCIDENCE OF THROMBO-EMBOLIC LESIONS ACCOMPANYING MYOCARDIAL INFARCTION

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IT HAS been pointed out that death in many cases of myocardial infarction is caused by subsequent thrombus formation or by the lodgment of emboli in other organs.¹⁻⁶ If the development of thrombi could be prevented, the mortality in cases of coronary occlusion might be significantly reduced.

Recently the use of anticoagulants after myocardial infarction has focused attention on this problem. Peters, Guyther, and Brambel⁴ were able to report a reduction of mortality in a group of fifty patients with myocardial infarcts treated with dicumarol. Moreover, there was only one embolus in fifty treated cases as compared with eight in a control series of sixty cases. Nichol and Page⁷ have reported similar results.*

Encouraging as this is, the present methods of preventing the formation of thrombi and emboli leave much to be desired. Both heparin and dicumarol are potentially dangerous agents and may easily do more harm than good unless given under expert supervision with continuous laboratory control. The tests for and control of the activity of the anticoagulants in the body have many pitfalls for the inexperienced.^{8,9} The dosage varies from patient to patient in an unpredictable manner. Hemorrhage requiring transfusion may occur,¹ and a few fatal cases have been reported.^{11,12} But these agents do lessen the danger of thrombus formation. The question remains as to whether the danger of thrombosis and embolism following an infarct of the myocardium is great enough to warrant the use of anticoagulant therapy.

MATERIAL

To evaluate the danger of thrombi and emboli following infarction of the myocardium, we have summarized reports from the literature and added statistics from an additional series of autopsied cases. Our material was taken from 2,000 consecutive autopsies performed at the Institute of Pathology, Western Reserve University, from 1935 to 1940. One hundred sixty-four cases of

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*Since this paper was submitted, another favorable report has appeared: Wright, I. S.: Experiences With Dicumarol (3,3' Methylene-Bis-[4 Hydroxycoumarin]) in the Treatment of Coronary Thrombosis With Myocardial Infarction, *AM. HEART J.* **32**:20, 1946.

recent and remote infarcts of the myocardium were encountered. The protocols of 160 of these presented sufficient data for critical analysis. There were 143 white and 17 Negro patients in the series. The ages ranged from 25 to 85 years with 72 per cent in the age group from 45 to 74 years (Fig. 1). The ratio of men to women was three to one. In Tables II, IV, and VI our results are added to those of the literature.

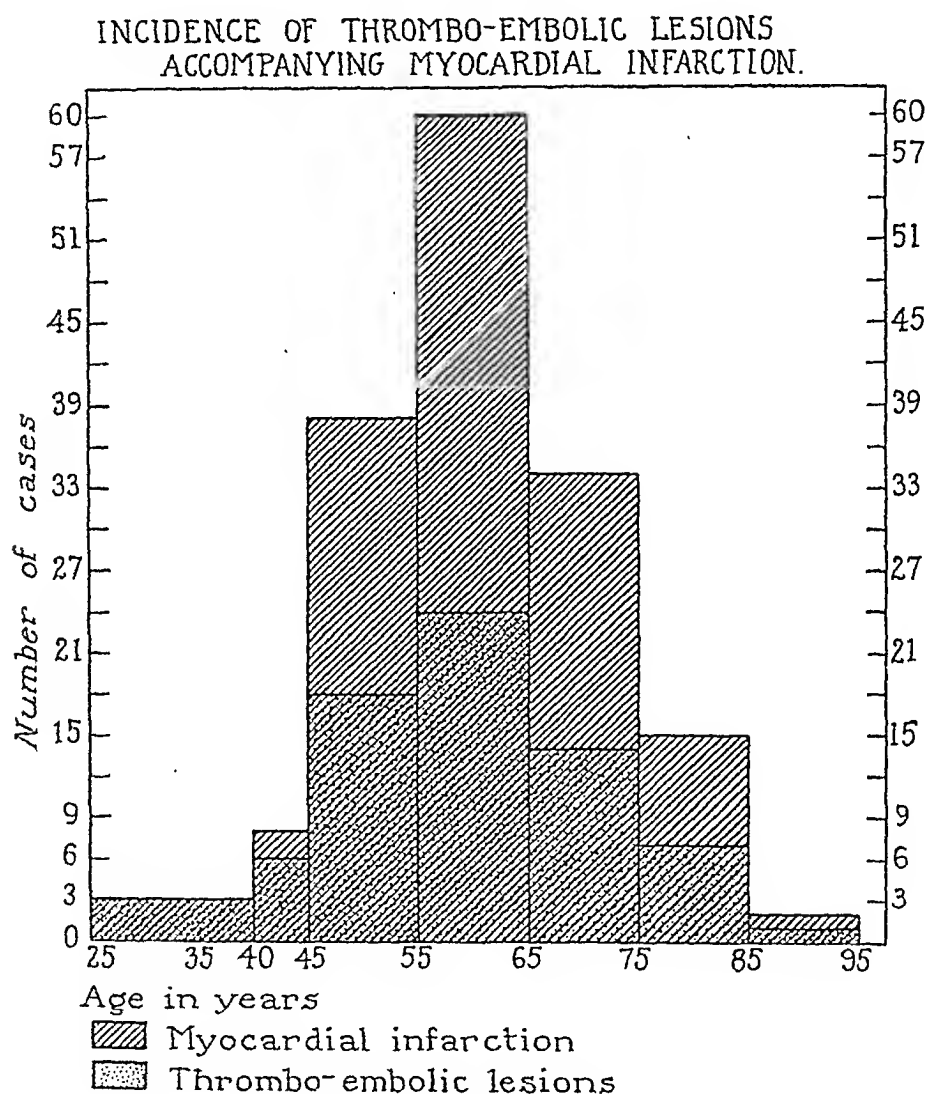


Fig. 1.

ANALYSIS OF MATERIAL

Incidence of Thrombo-Embolic Lesions in Myocardial Infarction.—In 1937 Blumer¹³ reported 945 cases of myocardial infarction (770 from the literature and 175 in his own series). Clinically detectable emboli or thrombi were found in 132. Since that time we have been able to add 655 cases from later reports.

The incidence of clinically detectable thrombo-embolic lesions* for the entire group is 11.5 per cent (Table I). In our autopsy series of 160 cases of myocardial infarct, 73 (45 per cent) had a total of 111 peripheral infarcts. There were 52 men and 21 women, approximately the same sex ratio as in the total series. The age incidence of thrombo-embolic lesions roughly follows that of myocardial infarction (Fig. 1). The number of cases of the younger age groups is too few for critical analysis, as over 90 per cent of the patients were more than 45 years of age. In the older groups the percentage of thrombo-embolic lesions is approximately 43 per cent.

TABLE I. PERIPHERAL INFARCTS AFTER MYOCARDIAL INFARCTION (CLINICAL CASES)

AUTHORS	CASES WITH MYOCARDIAL INFARCTS	CASES WITH PERIPHERAL EMBOLI OR INFARCTS
Anderson ²⁶	9	1
Blumer ¹³	175	27
Conner and Holt ²⁷	287	42
Gordinier ²⁸	13	3
Howard ²⁹	165	17
Hyman and Parsonnet ³⁰	51	17
Levine ³¹	145	17
Master and associates ³²	500	29
Nay and Barnes ³	100	14
Parkinson and Bedford ³³	100	8
Peters and associates ⁴	60	10
Total	1,605	185 (11.5%)

Etiological Factors.—In considering the heart as a source of emboli causing peripheral infarction, we have divided our cases into two groups for analysis: (1) those with mural thrombi within the heart and (2) those without intracardiac thrombi at autopsy. It is recognized that the absence of thrombi at autopsy does not preclude the possibility of their presence and dislodgment during life.

There were sixty-five cases (41 per cent) with intracardiac mural thrombi. This agrees closely with reports in the literature (Table II). Of these, thirty-six (55 per cent) showed peripheral occlusion of vessels from either thrombi or emboli. There were ninety-five cases without intracardiac thrombi. Thirty-seven, or 39 per cent, had distal occlusion of vessels of a thrombotic or embolic nature. This last figure is important as it indicates the tendency for the occurrence of thrombo-embolic processes in organs distal to the heart in cases where the heart does not appear to serve as a source of emboli. There may be local thrombus formation secondary to altered coagulability and decreased blood flow. Also,

*In this paper the term thrombo-embolic lesions indicates infarcts of various organs due to arterial occlusion caused by thrombosis or embolism. Because the distinction between emboli and thrombi is often impossible to establish, the inclusive term thrombo-embolic lesion is used. Also included are several cases of pulmonary and cerebral embolism in which death occurred before infarction could develop.

emboli to the lung need not come from the right side of the heart, but in many instances may originate in the veins of the legs. Bean¹⁴ found that massive emboli occluding the lumen of the pulmonary artery were always derived from the systemic veins. The leg veins were the source of massive pulmonary embolism in two of our cases. Thrombi in the right auricle were responsible in four other cases and in the twenty-seven remaining cases the origin was problematical as the leg veins were not routinely explored at autopsy.

TABLE II. INCIDENCE OF MURAL THROMBI AFTER ACUTE MYOCARDIAL INFARCTION PROVED BY AUTOPSY

AUTHORS	NUMBER OF AUTOPSIES	NUMBER OF CASES WITH MURAL THROMBI
Appelbaum and Nicolson ³⁸	150	81
Bean ¹⁴	300	142
Levine and Brown ³⁵	46	38
Lisa and Ring ³⁷	100	34
Meakins and Eakin ³⁶	62	29
Parkinson and Bedford ³³	83	14
Wolff and White ³⁴	23	7
This series	160	65
Total	924	410 (44.0%)

The incidence of thrombophlebitis of the lower extremities following infarction of the myocardium is 6.1 per cent in the reports listed (Table III). It is likely that the occurrence of unrecognized phlebothrombosis is even greater. It is probable that a large percentage of the emboli to the lung come from the leg veins¹⁵ and not from the right side of the heart.

TABLE III. THROMBOPHLEBITIS OF EXTREMITIES COMPLICATING MYOCARDIAL INFARCTION

AUTHORS	NUMBER OF CASES	THROMBOPHLEBITIS	AUTOPSY OR CLINICAL DATA
Harrington and Wright ³⁹	148	5	Clinical
Meakins and Eakin ³⁶	62	9	Autopsy
Nay and Barnes ³	100	7	Clinical
Parkinson and Bedford ³³	83	3	Autopsy
Total	393	24 (6.1%)	

But, regardless of the course of the emboli, there can be no doubt that decreased blood flow in the lungs is a factor of great importance in producing true pulmonary infarcts. In our series, passive hyperemia of the lungs, usually marked, was found in each case of pulmonary infarction. In four cases, massive pulmonary embolism resulted in sudden death before infarcts developed.

Location.—Table IV gives the location of peripheral thrombo-embolic lesions in 1,146 autopsied cases of infarction of the myocardium. Since some patients had more than one thrombus or embolus the total number given in the table is not the same as the number of patients so affected. In our series of 160

TABLE IV. THROMBO-EMBOLIC LESIONS FOLLOWING MYOCARDIAL INFARCTION (AUTOPSIED CASES)

AUTHORS	NUMBER OF AUTOPSIES	TOTAL THROMBO- EMBOLIC LESIONS	LUNGS	BRAIN	KIDNEY	SPLEEN	EXTREMITIES	CAROTID OR AORTA	MESENTERY
Bean ¹⁴	300	116	43	15	29	17	8	1	3
Eppinger and Kennedy ⁵	200	—	46	—	—	—	—	—	—
Garvin ⁶	133	128	45	18	32	19	11	0	3
Kugel and Lichtman ¹¹	95	—	33	—	—	—	—	—	—
Meakins and Eakin ²⁶	62	87	47	4	14	9	11	2	0
Parkinson and Bedford ³³	83	31	7	1	9	8	2	1	3
Saphir and associates ⁴⁰	34	20	10	(All others, 10)					
Wolff and White ³⁴	19	11	0	2	6	2	0	0	1
Woods and Barnes ²	60	15	6	9	0	0	0	0	0
This series	160	111	33	14	28	17	13	0	6
Total	1,146								
Per cent with lesions*			23.5	7.7	14.4	8.8	5.5	0.5	1.9

*Percentages are calculated from the series in which complete data are available.

cases, 73 had a total of 111 peripheral thrombo-embolic lesions. That is, of 160 patients examined at postmortem with myocardial infarcts, 45 per cent had emboli or thrombi in other parts of the body. Table V shows the localization of peripheral thrombo-embolic lesions in cases with and without intracardiac thrombi.

A further division of the thirty-three cases of pulmonary thrombo-embolism is as follows: in twenty-one cases only one lobe was the seat of infarction as a

TABLE V. LOCALIZATION OF THROMBO-EMBOLIC LESIONS IN CASES WITH AND WITHOUT INTRACARDIAC THROMBI

SITE	95 CASES WITHOUT MURAL THROMBI	65 CASES WITH MURAL THROMBI	TOTAL
Lungs	12	21	33
Kidneys	10	18	28
Spleen	12	5	17
Extremities	9	4	13
Mesentery	3	3	6
Brain	11	3	14
Total	57	54	111

result of thrombosis. The lower lobes were involved in seventeen of twenty-one cases, the right lower lobe twice as often as the left lower lobe. In eight cases more than one lobe was involved (five cases involving the right and left lower lobes, two cases the right lower and middle lobes, and one case the right middle and lower, and left lower lobes). In four cases no infarct developed because of the speed with which death followed the vascular occlusion. In an analysis of thirty-three cases of pulmonary infarction, Tiedemann¹⁶ found the right lower lobe involved in fifteen, the right upper lobe in seven, the left lower in five, the left upper in four and the right middle in two. Bean¹⁴ similarly noted that pulmonary infarcts were most frequent in the lower lobes.

Severity and Significance.—The figures of Table IV are incomplete in that the extent and severity of the peripheral thrombo-embolic lesions are not mentioned. In most instances, it was impossible to gather such complete data from the literature, but the authors listed in Table VI do show thrombo-embolic lesions of lungs as the main cause of death in 10.6 per cent of the cases studied. In eight of our cases (Table VII), death was caused directly and immediately by massive occlusion of the pulmonary artery or its main branches (main pulmonary artery in one case, right pulmonary artery three cases, left pulmonary artery one case, arteries to both lower lobes two cases, and smaller branches of all lobes one case). In thirteen additional cases pulmonary infarction was contributory to death but secondary to vascular occlusion in the heart or other organs. In twelve cases pulmonary infarction was probably of minor significance.

TABLE VI. THROMBO-EMBOLIC LESIONS OF LUNGS AS A CAUSE OF DEATH AFTER MYOCARDIAL INFARCTION

AUTHOR	CASES STUDIED	DEATHS	DEATHS FROM THROMBO-EMBOLIC LESIONS OF LUNGS	PER CENT OF DEATHS FROM THROMBO-EMBOLIC LESIONS OF LUNGS
Eppinger and Kennedy ⁵	200	200	13*	6.5
Master, Dack, and Jaffe ³²	500	144	29	20.0
Peters, Guyther, and Brambel ¹	60	13	6	46.0
Woods and Barnes ²	128	60	6	10.0
This series	160	160	8	5.0
Total	1,048	577	62	10.6

*In an additional 35 cases, pulmonary emboli are listed as an important contributory cause of death.

In addition to the cases in which death was caused by pulmonary infarction, there were twenty-two other cases in which thrombo-emboli in other locations were the main or contributory cause of death. *Thus, in 48 of 160 cases it is certain that thrombo-embolic lesions were important as a cause of death.* This agrees closely with the observations of Eppinger and Kennedy⁵ who reported thrombo-embolic lesions following coronary thrombosis as a main or contributory cause of death in 49 of 200 cases.

TABLE VII. THROMBO-EMBOLIC PHENOMENA AS CAUSE OF DEATH IN 160 CASES OF MYOCARDIAL INFARCTION

ORGANS INVOLVED	MAIN CAUSE OF DEATH	CONTRIBUTORY CAUSE
Lung	8	13
Brain	3	5
Leg	3	3
Mesentery	2	
Leg and mesentery	1	
Lung, kidney, leg, mesentery and spleen	1	
Brain, mesentery, arm and leg	1	
Spleen, kidney and mesentery		1
Spleen and kidney		2
Total	19 Cases	24 Cases
Per cent total number cases	12	15

Generally, lesions of the mesenteric vessels, lungs and brain, or a combination of involvement of these structures, had the gravest clinical prognosis. Occlusion of the mesenteric vessels occurred in six cases of myocardial infarction, and resulted in death in five cases. In several cases the presenting symptoms were those of peritonitis or intestinal obstruction. Coexistent lesions in the legs or brain complicated the clinical picture in four cases. The superior mesenteric artery was occluded in three cases, twice by emboli, and once by thrombi; the inferior mesenteric once by embolism, and once by thrombosis.

Cerebral thrombo-embolic lesions were found in fourteen cases, of which two were embolic and twelve thrombotic. They were the immediate cause of death in three cases and contributory in five others. In eleven of the fourteen cases severe arteriosclerosis of the cerebral arteries was found with milder involvement of the arteries in the remaining three cases. Obviously, this cerebral vascular disease was more important in causing cerebral infarcts than were emboli from mural thrombi of the heart. As a matter of fact, eleven of the fourteen cases of cerebral infarct were found in persons without intracardiac thrombi. When the coronary arteries are sclerotic there is usually similar disease of vessels all over the body to a lesser degree. Once the heart is the seat of an infarct and factors favoring blood coagulation are brought into play, the chances are good for secondary thrombosis to occur in other locations.

This tendency to simultaneous thrombosis applies also to the extremities. Eight cases with mural thrombosis in the heart showed occlusion of the arteries to the extremities, but, there were also five cases in which there were thrombotic lesions of the leg arteries in the absence of intracardiac thrombi. There were only four of thirteen cases in which the diagnosis of embolism could be made. Arterial occlusion of the leg vessels is a serious complication and was the chief cause of death in three cases. There is frequent coincident involvement with other vital structures—brain, mesentery, and lungs (three cases).

Control.—In order to test the validity of our figures we have studied the incidence of thrombo-embolic phenomena in a control group of 100 cases in the

same autopsy series. The cases were selected at random from patients of a similar age, dying from causes other than myocardial infarction. Of the 100 control cases, fifteen showed thrombi or emboli.* After coronary occlusion the incidence of peripheral infarcts increases to 45 per cent. This is statistically significant.

DISCUSSION

The diagnosis of pulmonary infarction is clinically difficult as the diagnostic criteria usually mentioned in textbooks of medicine are rarely present. In our series, the clinical diagnosis of pulmonary embolism or infarction was made in only five of the thirty-three cases in which it was found at autopsy. In eight cases, the diagnosis of bronchopneumonia was erroneously made when pulmonary infarcts were present. In the other twenty the condition was unsuspected and no diagnosis other than myocardial infarction was made. A review of the clinical records of these cases examined at autopsy showed that often there were no signs or symptoms except those that might be ascribed to cardiac decompensation or myocardial infarction. In a few, however, the occurrence of slight chest pain, a rise in temperature, pulse, or respiratory rate might have led to the correct diagnosis. Hines¹ has reported an even lower percentage of clinical recognition. In his eighty-one cases of pulmonary infarct proved by post-mortem examination, only two were diagnosed before death. He also found similarity between the signs and symptoms of pulmonary infarction and heart failure. Hemoptysis, the best single sign, occurred in approximately 33 per cent of the cases with pulmonary infarction, while it was present in 8 per cent of those with uncomplicated cardiac failure.

We do not fully understand why there should be a greater tendency for the development of thrombi in parts distal to the heart after a myocardial infarct. Undoubtedly many factors are involved. The same undetermined elements that favor the occlusion of the coronary artery must also operate in the peripheral vessels before the cardiac infarct occurs. Many cases of myocardial infarction showed coexistent thrombosis of the extremities, mesentery, kidneys, spleen, and cerebral arteries. These lesions paralleling the development of the coronary thrombosis must have had a similar pathogenesis.

After myocardial infarction the tendency of the blood to clot is further accelerated in the following ways. There is increased viscosity of the blood with the hemoconcentration accompanying shock and congestive heart failure.¹⁷ The blood pressure falls and there is a slowing of the venous flow concomitant with the decrease in the cardiac output. A decrease in the movement of the legs with enforced bed rest and limitation of the respiratory excursion further increases the peripheral venous stagnation. A decrease in the dilute prothrombin time has been observed following myocardial infarction.^{18,9} There is some question as to whether the drugs used in treatment may not increase the clotting tendency of the blood. Digitalis^{19,21} aminophylline,²² mercupurin, salyrgan,

*In two cases, thrombi were associated with contiguous inflammation (mastoiditis and meningitis). One had rheumatic heart disease and auricular fibrillation. In one case, emboli originated from the leg veins, associated with fracture.

mercuryhydri²³ and penicillin^{23,24} have all been implicated. Recent workers, however, have found digitalis to have no effect on blood clotting as measured by prothrombin times.²⁵ The final answer must await further investigation.

On the basis of the data presented, it is evident that vascular thrombi and emboli are serious complications of myocardial infarction. If the intravascular clotting can be reduced, the incidence of mural thrombosis of the heart itself with resultant embolism and independent coexistent peripheral thrombosis will decrease. The many patients who now die of secondary infarcts of the lung, brain, and mesentery may recover from the primary myocardial lesion and survive for a number of years. It is our opinion, therefore, that the carefully controlled, intelligent use of anticoagulant agents after myocardial infarction deserves an extensive clinical trial.

SUMMARY

1. The incidence and severity of thrombo-embolic lesions following myocardial infarction has been studied in 160 cases of myocardial infarction encountered in a series of 2,000 consecutive autopsies.

2. Of the 160 cases of myocardial infarction 73 (45 per cent) had a total of 111 thrombo-embolic lesions.

3. Peripheral infarcts were a main or contributory cause of death in 43 of 160 cases.

4. The use of anticoagulants is thought to be warranted when proper control is available.*

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AN EXPERIMENTAL METHOD FOR THE CLOSURE OF INTER-AURICULAR SEPTAL DEFECTS IN DOGS

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THE purpose of this paper is to describe a method for the closure of interauricular defects in dogs. The procedure, which will be described, is based upon a suggestion made by Dr. J. K. Lewis of the Department of Medicine.

METHODS

Production of Interauricular Septal Defect.—Using intratracheal positive pressure anesthesia, the left side of the chest of the dog was opened. The lung was packed away and the pericardium exposed. The pericardium was opened and the left auricular appendage was brought into the wound. Two straight clamps were placed on the edge of the auricular appendage in such a fashion that a V was formed. The auricle was opened between the legs of the V. Opening the auricle in this way facilitated the control of hemorrhage. A curved clamp was then inserted into the left auricle until the septum was felt. The clamp was forced through the septum, opened, and then withdrawn. A silk tie was placed around the base of the two clamps which were then removed from the auricular appendage.

By this method a defect was produced in the septum which varied from 4 to 6 mm. in diameter. The resulting defect was invariably circular. The dogs were in no way disturbed by this procedure.

Closure of the Septal Defect.—After a period of two weeks had elapsed, repair of the septal defect was undertaken. With the dog under positive pressure intratracheal anesthesia, the right side of the chest was opened and the right auricle identified after the pericardium had been incised. By gently pushing the right auricle toward the septum, with practice one can feel the defect. When the wall of the auricle is in contact with the septum, a stitch is placed through the wall of the auricle, through the septum, and out through the wall of the auricle, as shown in Fig. 1. The stitch is then pulled up and tied. If possible, a second stitch is placed close to or into the defect. At this stage of the operation the heart rate usually becomes irregular. The distorted auricular wall now partially obstructs the vena cava. Next, a wire threaded on a needle is introduced into the auricle and made to encircle completely the part of the auricle which has

been attached to the septum; the two ends of the wire are made to enter and emerge from the auricle at the same point. These steps are shown in Figs. 2 and 3. After the wire is in place, a running silk stitch is placed in the auricle and made to encircle the portion of the auricle which has been attached to the septal defect. This stitch is carried up to the point where the wires emerge from inside the auricle. Tightening the running stitch brings surrounding portions

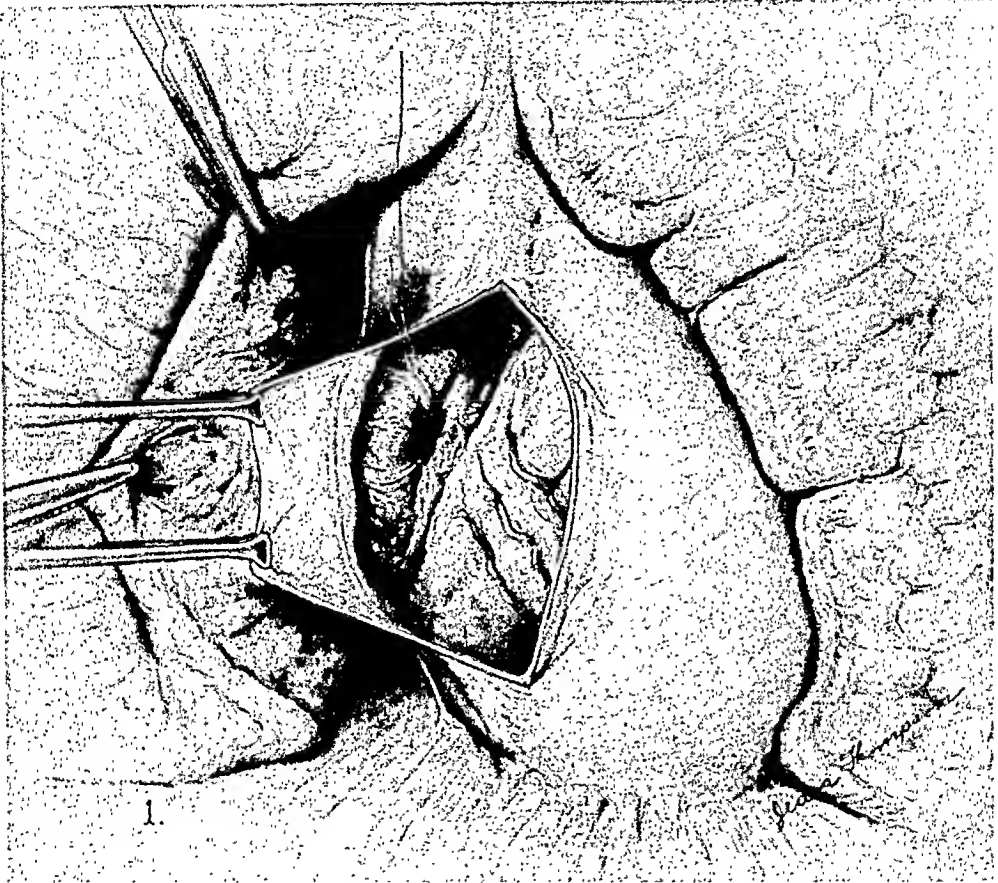


Fig. 1.—A drawing which shows the introduction of the suture from the outside of the right auricular wall which attaches a portion of the auricular wall to the septum and partially closes the defect. If possible, a second suture is similarly introduced in order to close the defect more effectively.

of the auricular wall together and buries the portion which is closing the defect, just as an appendix stump is buried. An ordinary tonsil snare is then used to pull the wires through the auricular muscle and to cut off the portion of the wall of the auricle which has been anchored to the septum. The small hole which was occupied by the snare is quickly closed by continuing the running silk stitch. The end result is shown in Figs. 5 and 6. The wire must be fairly heavy to cut through the muscular auricular wall of the dog.

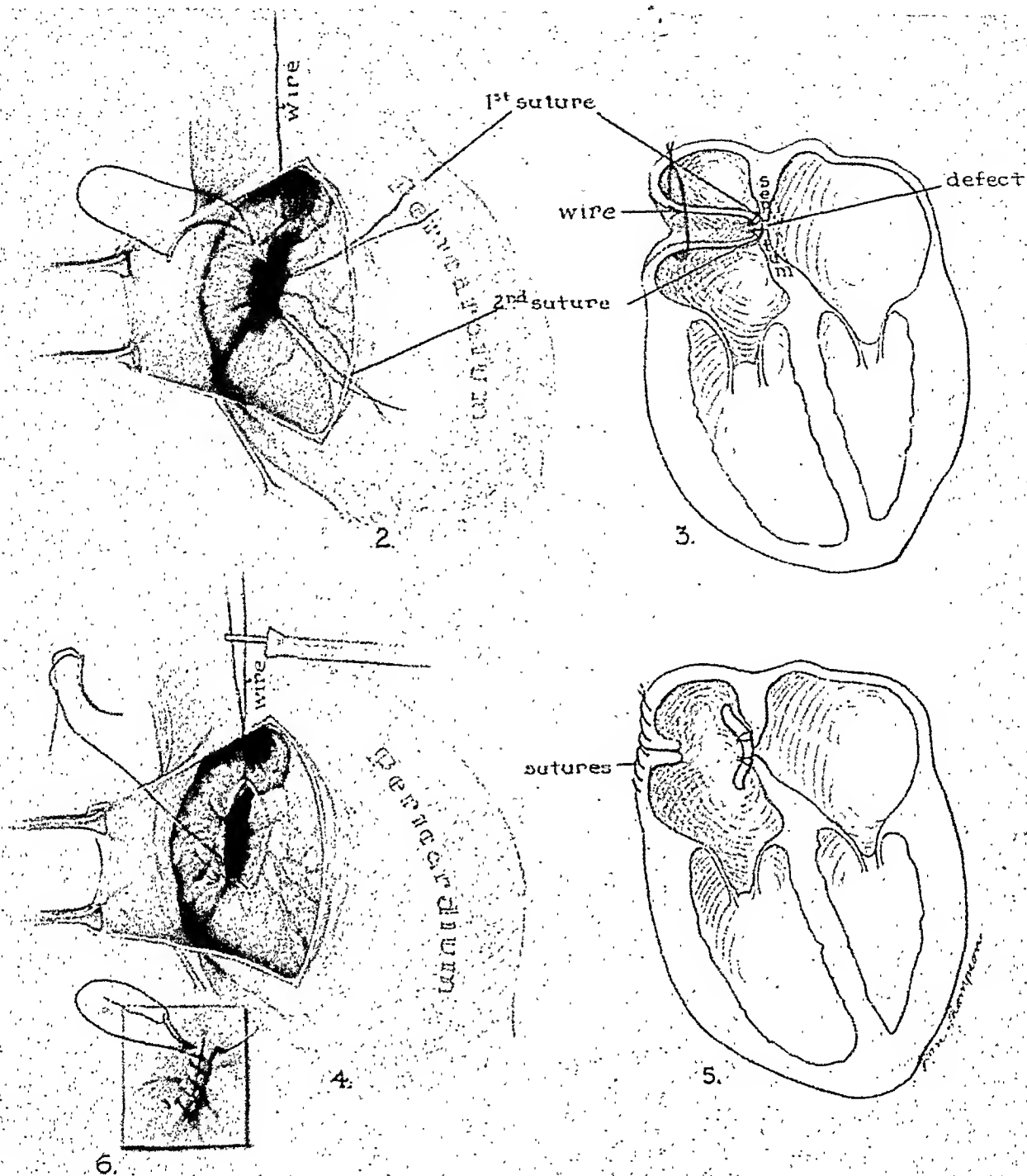


Fig. 2.—A drawing which shows the beginning of the introduction of the steel wire into the auricular muscle. The wire will be made to surround the portion of the muscle sutured to the interauricular septal defect.

Fig. 3.—A drawing showing the relation of the steel wire to the portion of the auricular wall attached to the septal defect.

Fig. 4.—A drawing which shows the completely introduced steel wire and the beginning of the introduction of the running silk suture.

Fig. 5.—A drawing showing the detached portion of the auricular wall which closes the septal defect.

Fig. 6.—A drawing showing completion of the closure of the auricular wall externally.

RESULTS

An interauricular septal defect has been produced and closed in eight dogs. Five of the dogs survived the operation without apparent incident. Two dogs died from hemorrhage, and the heart of one dog stopped beating while it was being handled.

At the end of one month the five surviving animals were sacrificed. A collection of tissue was present on the septal wall which microscopically consisted of scar tissue and auricular muscle. A smooth scar was noted on the inside of the auricular wall at the site of the running silk stitch. In no instance were the valves of the right ventricle deformed by the procedure, but in two of the five dogs the button of tissue appeared to be large enough to impede the stream of blood from the superior vena cava. The dogs, however, appeared to be clinically well.

DISCUSSION

In the human heart interauricular septal defects result in great dilation of the right auricle. It might be simpler to perform an operation, similar to the one described in this paper, on the large human auricle than on the small auricle of

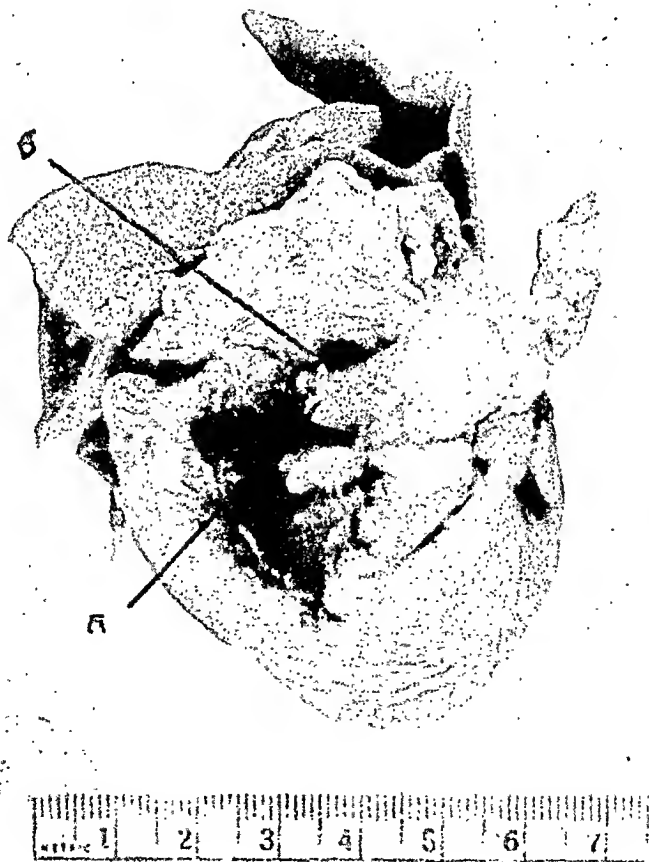


Fig. 7.—A photograph of the interior of the auricle of a dog sacrificed one month after operation. A, A drawing which shows the size of the detached portion of the auricular wall which closes the defect. B, The suture line on the inner aspect of the auricular wall is also shown.

the dog. While auricular septal defects, which produce symptoms in patients, are much larger than those artificially produced in the dog,¹ it is possible that they might be closed just as easily since the human right auricle is also much larger. The dog's auricle, however, is a muscular structure and sews more easily than the human auricle.

In the dog it is apparently not necessary to anchor the attached auricular muscle completely across the defect. The trauma caused by the sutures near the defect seems to cause enough thrombus to form around the attached muscle to complete the closure of the defect.

Fig. 7 is a photograph of a dog's heart showing the size of the button of tissue found thirty days after operation, *A*, and the suture line on the inner aspect of the auricular wall, *B*.

SUMMARY

A method is described whereby a defect in the interauricular septum in dogs can be closed.

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TOLERANCE OF THE HUMAN HEART TO ACIDOSIS; REVERSIBLE CHANGES IN RS-T INTERVAL DURING SEVERE ACIDOSIS CAUSED BY ADMINISTRATION OF CARBON DIOXIDE

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DURING the course of a study on the effects of increased blood carbon dioxide on mental disease, severe acidosis was regularly produced in patients. In two of the patients electrocardiograms were made, and these revealed striking though transitory changes. Since intolerance of the mammalian heart to acidosis was reported several decades ago^{1,2} and since a recent publication demonstrates a greater tolerance,³ it was considered of interest to record the changes observed here.

MATERIAL AND METHODS

Two psychotic women patients, aged 80 and 46 years, respectively, were studied. Electrocardiographic observations were made during seven experiments over a twenty-five day period on one patient and on one occasion in the other. The initial electrocardiograms in the first patient showed evidence of an old healed myocardial infarct in the CF leads but not in the limb leads.

The patients were given 15 mg. of morphine sulfate subcutaneously approximately one-half hour prior to the experiment. Curare,* 0.85 unit per pound of body weight, was given intravenously, the injection taking two minutes. Immediate disappearance of the cough and gag reflexes occurred and two or three minutes later respiration stopped. As soon as coughing and gagging became impossible and before respiration ceased, a Magill catheter was inserted into the trachea at a level estimated to be 3 or 4 cm. above the carina. A mixture of 5 per cent carbon dioxide and 95 per cent oxygen was administered at a rate of 5 to 6 liters per minute. Complete apnea lasting for ten or twenty minutes ensued, with occasional hiccoughing. During the next ten to thirty minutes the hiccoughs deepened and became convulsive gasping breaths. Efficient breathing began thirty to sixty minutes after the injection of curare. The cough and gag reflexes returned fifteen to thirty minutes later, at which time administration of the carbon dioxide-oxygen mixture was terminated. The duration of administration was forty-five to ninety minutes.

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When the mixture of carbon dioxide and oxygen as allowed to flow at a rate of 5 or 6 liters per minute from the tank through the catheter, the pressure in the latter was plus 2 cm. of water. When, however, the catheter was placed in the trachea the pressure was between plus 6 and plus 8 cm.; during hiccoughs it returned momentarily to atmospheric. When respiration was re-established, negative pressures were developed with each inspiration; respiration was hyperpneic and pressures as low as minus 20 cm. were recorded in inspiration.

Limb, CF, and V lead electrocardiograms were made before, during, and after administration of the mixture of carbon dioxide and oxygen. Samples of arterial blood were taken over mercury and analyzed for oxygen and carbon dioxide by the method of Van Slyke and Neill⁴ slightly modified.⁵ The pH was measured by means of a glass electrode.

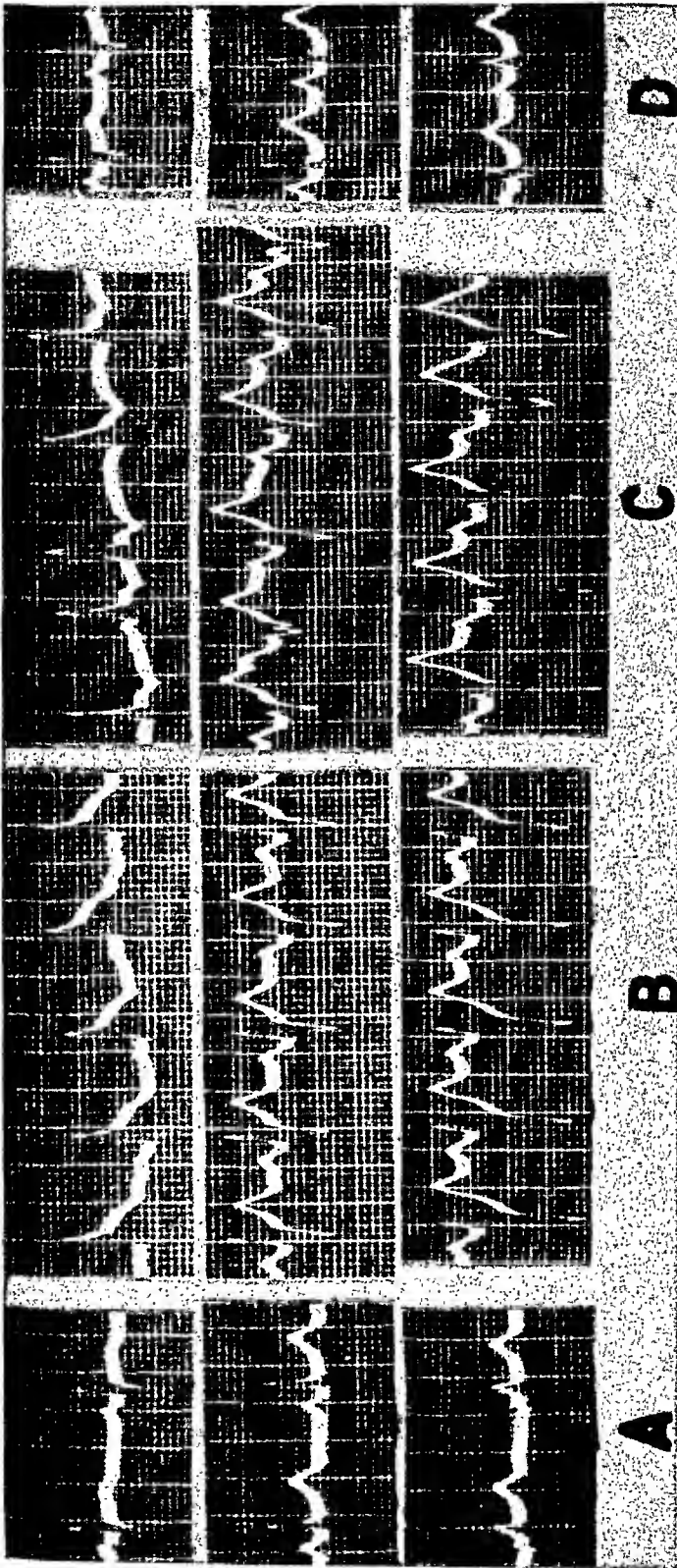
OBSERVATIONS

The control values for arterial blood oxygen lay between 18.85 and 21.59 volumes per cent and for carbon dioxide, between 42.25 and 45.34 volumes per cent. The initial pH was between 7.40 and 7.42. During administration of the gas mixture the arterial blood oxygen was between 20.70 and 22.54 and the carbon dioxide, between 50.70 and 58.60 volumes per cent. The arterial blood pH was between 6.81 and 7.03 and averaged 6.89.

The cardiac rate was accelerated during the administration of the carbon dioxide and oxygen mixture; the P-R interval did not change appreciably. A-V nodal beats appeared. Some increase in the height of the R and T waves occurred. In one patient (Case 2) Q_1 became prominent. On the occasion of the first administration of the carbon dioxide-oxygen mixture in both patients, elevation of ST_1 and depression of ST_3 developed; T_1 or T_3 became inverted (Figs. 1, *B* and 2, *B*). Within thirty minutes after the cessation of administration of the carbon dioxide-oxygen mixture these changes had largely or entirely disappeared (Fig. 2, *C*). In the patient (Case 1) studied during repeated experiments, similar though less marked changes in S-T segment of the limb leads occurred during the second experiment (Fig. 1, *C*), and none at all during the third or subsequent experiments (Fig. 1, *D*). However, Leads CF and V (Fig. 1, *E* and *F*) did show changes in V waves and S-T segments at this time. This variation in the appearance of evidences in the limb leads of injury to the myocardium was not associated with lessened changes in arterial blood carbon dioxide or pH during the later experiments.

DISCUSSION

As was recently pointed out by Gertler, Hoff, and Humm,³ the mammalian heart is much more tolerant to acidosis than was formerly believed. These authors found no evidence of cardiac damage in dogs until the arterial blood pH fell to between 5.9 and 6.7. In the present study in man, changes in RS-T interval and inversion of T waves suggestive of a current of injury became detectable at higher pH levels, but even these were considerably lower than levels of pH encountered in acidosis in clinical practice. Gertler and co-workers³



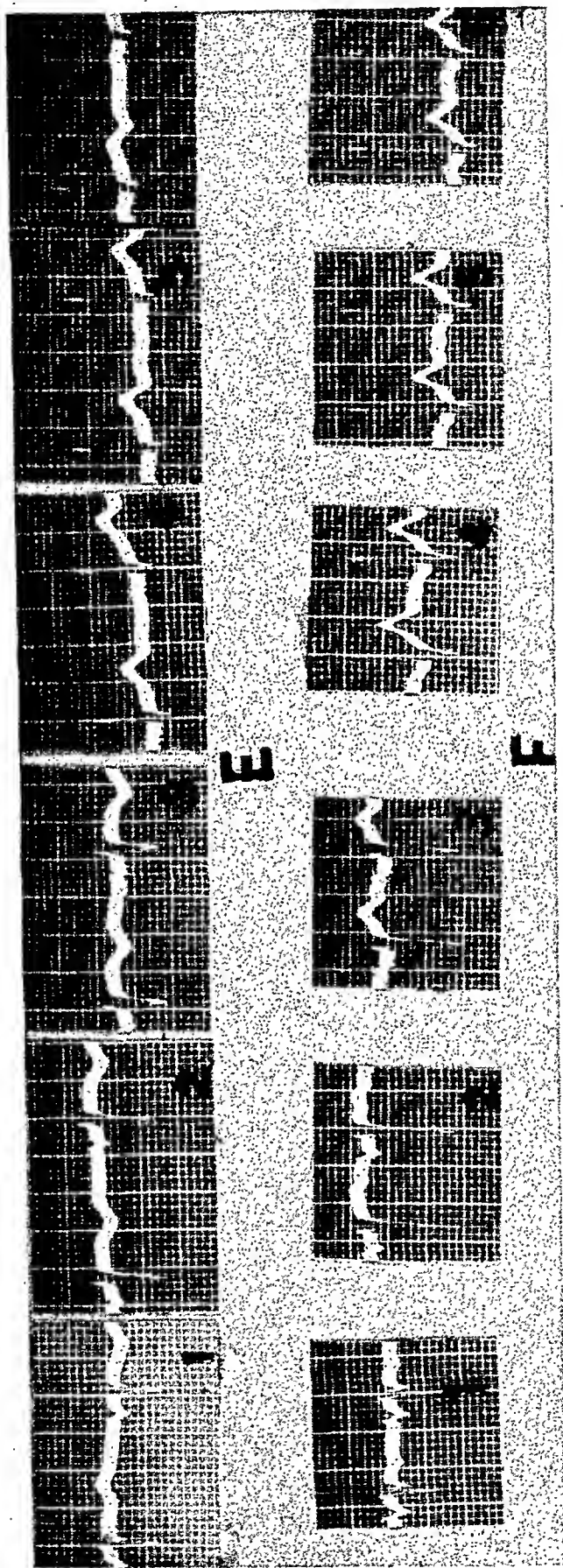


Fig. 1.—Case 1. Effect of 5 per cent carbon dioxide and 95 per cent oxygen. *A*, Control electrocardiogram; *B*, during administration of the gas mixture the first time; *C*, during administration of the gas mixture the second time; *D*, during administration of the gas mixture the third time; *E*, control V lead electrocardiogram during seventh experiment; *F*, effect on V leads of administration of the gas mixture the seventh time.

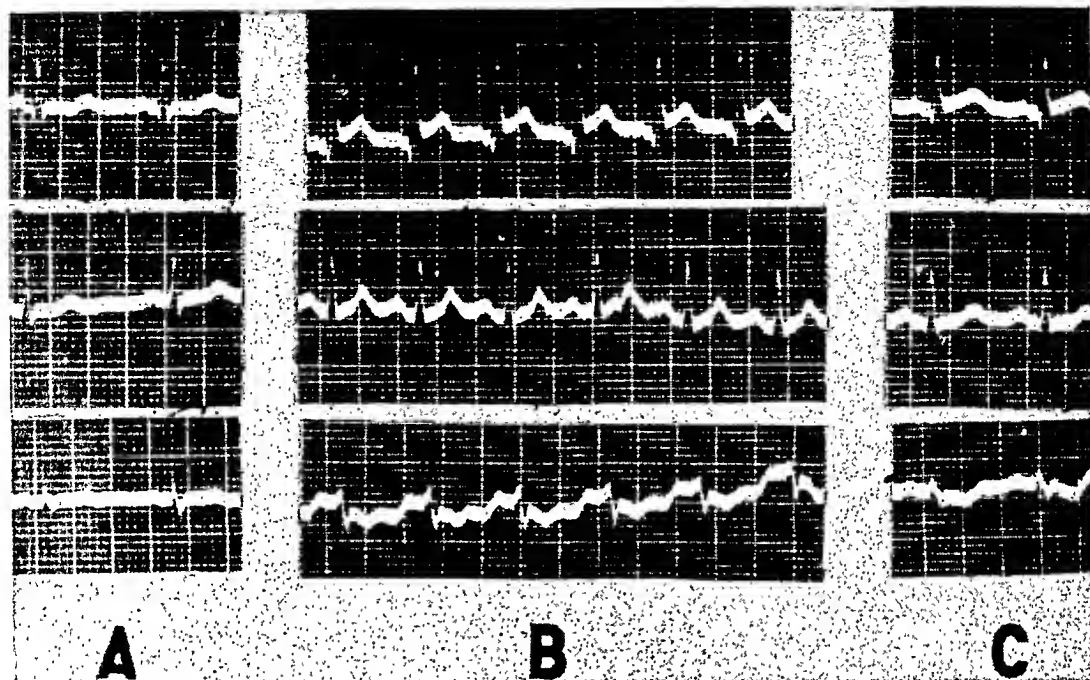


Fig. 2.—Case 2. Effect of 5 per cent carbon dioxide and 95 per cent oxygen. A, Control electrocardiogram; B, during administration of the gas mixture; C, twenty minutes after end of administration.

recorded only the second lead of the electrocardiogram and so may possibly have missed changes in the other leads at a higher blood pH. On the other hand, attempts made here to produce similar changes in RS-T interval and inversion of the T waves in dogs by means of a procedure similar to that practiced in the human subjects were unsuccessful.⁶ It appears, therefore, that the human heart is less tolerant to acidosis than the canine.

Gertler and associates³ concluded that the appearance of evidence of the current of injury in the acidotic dog was a terminal event, but the observations of the present study do not support this concept. Indeed, in both patients studied here it was clear that the changes were rapidly reversible after administration of carbon dioxide was discontinued, and in the one patient studied during seven consecutive experiments evidences of injury were less marked in the later ones. It is of interest in this connection that the development after a time of tolerance to carbon dioxide has also been noted in animals.¹¹ Clinically, all patients given carbon dioxide in the manner reported, including the two described here, remained active and well in every way; one of them, aged 80 years, subsequently was able to stand, without untoward event, the cardiac strain of a course of electrically induced convulsions given to cause remission of her psychosis. Similarly, the conclusion of Gertler and associates,³ that the injury of acidosis is limited largely to the right ventricle, is not supported by the electrocardiograms obtained here.

As in the case of the observations of Gertler, Hoff, and Humm,³ the present study showed no indication of the development of impaired auriculoventricular contraction during acidosis, although evidence of vagal hyperactivity in the form of A-V nodal beats did appear in the earlier experiments. The unexplained

increases in the amplitudes of the R and T waves noted by earlier workers^{2,3,7,8} were also observed here.

The development of marked changes in RS-T segment in the absence of anoxia here and also apparently in the experiments of Gertler and co-workers³ is worthy of comment in view of the fact that it has become customary in clinical practice to refer to this change as anoxic or ischemic in origin. It is to be noted that the arterial blood oxygen content was high at the time of the appearance of the abnormalities in the electrocardiogram and that other factors also operated to raise tissue oxygen tension. These additional mechanisms were increased blood flow to the tissues⁹ and increased dissociation of oxyhemoglobin brought about by carbon dioxide acidosis. The question naturally arises as to whether the high concentration of oxygen administered in the present experiments might have given rise to generalized vasoconstriction, thereby producing ischemic changes in the tissues.¹⁰ There is no evidence that such generalized vasoconstriction does occur in the presence of increased oxygen tensions, and, moreover, even small increases in carbon dioxide tension are sufficient to obliterate any tendency to localized vasoconstriction that might occur.¹⁰

SUMMARY AND CONCLUSIONS

Intratracheal administration in man of a mixture of 5 per cent carbon dioxide and 95 per cent oxygen caused lowering of the arterial blood pH to the neighborhood of 6.9 and was associated with changes in electrocardiogram indicative of myocardial injury. These changes were rapidly reversible after cessation of each experiment and decreased in severity when experiments were repeated several times in the same patient. The human myocardium, though more tolerant to acidosis than was formerly believed, appears, however, to be less tolerant than the canine heart.

Electrocardiographic changes considered to be consequent to anoxia or ischemia may occur when arterial blood oxygen content is high and other factors, also making for increased tissue oxygen tensions, exist.

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THE INFLUENCE OF HEART SIZE ON THE CIRCULATION TIME

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FOLLOWING the reports of Blumgart,¹ considerable attention has been given to measurement of the velocity of blood flow, and many methods have been introduced for the estimation of the circulation time. Most of the reports include the description of a method and its application to patients with compensated and decompensated heart disease and to patients with various conditions which influence blood velocity such as hyperthyroidism, hypothyroidism, polycythemia, and anemia.

The most consistent abnormality noted is a prolongation of the circulation time in decompensated heart disease. It is generally stated that in compensated heart disease the velocity of blood flow is within normal limits, and it is suggested that the circulation time may be utilized as an index of the presence and degree of heart failure. A review of the circulatory measurements in various reports indicates, however, that complete consistency does not exist between the circulation time and the presence or degree of cardiac decompensation.

Blumgart found a prolonged circulation time in some individuals with hypertension who showed no evidence of congestive failure. This was explained as the result of a back pressure effect on the pulmonary vessels by the hypertension. As evidence supporting this theory, experiments were cited in which compression of the aorta caused dilatation of the alveolar capillaries of the lungs with resulting slowing of the circulation. Robb and Weiss² state that "a correlation of the results of circulatory measurements with the degree of disability of the patients failed to reveal a strict relationship." These observers found a normal circulation time in some cardiac patients in whom clinical, x-ray, and vital capacity findings were characteristic of stasis in the pulmonary circulation. They postulated that the dyspnea and reduced vital capacity were caused primarily by an increased pressure in the pulmonary vascular bed and that this pulmonary hypertension prevented a slowing of the blood flow. Baer and Slipakoff,³ using calcium gluconate, found that approximately 30 per cent of cardiac patients with prolonged circulation times did not have obvious heart failure. They concluded

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that in certain cases an abnormal circulation time predicted the onset of cardiac failure. Wall,⁴ also using calcium gluconate, observed that all patients with congestive failure showed circulation times in excess of 20 seconds. He noted, however, that there were circulation times longer than 20 seconds in cardiac patients who presented no evidence of heart failure. Using magnesium sulfate, Neurath⁵ found circulation times of 11 to 17 seconds in normal persons, 12 to 26 seconds in patients with hypertension without decompensation, and 13 to 58 seconds in patients with hypertension with cardiac decompensation. Hussey, Wallace, and Sullivan,⁶ in a study of 100 cardiac patients, found fifteen in whom the circulation time was prolonged in the absence of any manifestations of heart failure. They discussed errors in technique in carrying out the procedure as a possible explanation.

It is apparent that there is not a uniformly consistent relationship between the clinical condition of the cardiac patient and the circulation time. The discrepancy observed most frequently is the presence of a prolonged circulation in individuals who show no evidence of heart failure. It is clear also that there is no general agreement as to the explanation of this discrepancy.

Several years ago a study was made of a patient with extreme cardiac enlargement secondary to chronic rheumatic valvular disease. Although this patient showed no definite evidence of cardiac decompensation, markedly prolonged circulation times were obtained by several methods. The study of this patient suggested that cardiac dilatation per se has an important influence on the circulation time.*

The patient, a 47-year-old woman, has been under observation for about fifteen years. There was a history of rheumatic fever at the age of 12 and again at the age of 18 years. At the age of 15 years, she was told that her heart was affected and her activities were moderately restricted. When first seen there was a blowing systolic murmur and a late diastolic murmur at the apex. There was a marked generalized dilatation of the heart and an extreme dilatation of the left auricle as seen fluoroscopically in the right lateral position. At no time has there been any evidence of decompensation. She has carried on moderate social activities, has supervised her home, and, for a time, participated in a business venture with an associate. In the past ten years auricular fibrillation has been present and the ventricular rate has been controlled by small maintenance doses of digitalis, 0.5 cat unit a day. In the past year there have been periods of dysphagia apparently due to pressure on the esophagus by the dilated left auricle. On examination, there was no dyspnea, orthopnea, or cyanosis. The heart was markedly enlarged to the right and left. The heart rate was 68, the rhythm was totally irregular, and there was a blowing systolic murmur at the apex. The blood pressure was 114 systolic and 80 diastolic.

There was no evidence of passive congestion of the lungs, and the liver was not palpable. There was no peripheral edema. On fluoroscopic examination the heart shadow practically filled the chest. In the right lateral position the left auricle extended posteriorly far beyond the spine. The barium-filled esophagus was compressed and displaced posteriorly beyond the spine (Fig. 1).

On one occasion the venous pressure was 86 mm. H₂O, the ether circulation time was 7 seconds, and the saccharine time, 1 minute, 12 seconds. About a month later the ether time was 9.5 seconds; after the injection of saccharine a slight sweet taste was noted after 2 minutes, 7 seconds. The circulation was then studied by the use of fluorescein, which is an objective method.⁷ A histamine wheal was first applied to the left forearm. After the injection of 2 c.c. of 20 per cent

*This study was reported before the California Heart Association by one of the authors (M. H. N.) May 6, 1944, under the title, "Factors Influencing Circulation Time."



Fig. 1.—Patient R. R. Teleroentgenogram and right lateral view with barium-filled esophagus showing marked dilatation of the left auricle.

sodium fluorescein, the first appearance of fluorescence in the conjunctivae occurred at 62 seconds and in the wheal on the forearm at 64 seconds. The normal arm-to-conjunctiva time by this method is 12 to 15 seconds. Following these studies the patient has been under observation for two years and there has been no change in her clinical condition.

This patient illustrates a striking discrepancy between the circulation time and the functional state of the heart. A markedly prolonged circulation time is present in the absence of symptoms and signs of congestive failure. The cardiac enlargement is due chiefly to an extreme dilatation of the left auricle. The average normal content of the left auricle is 140 cubic centimeters. It is known that a volume of 2 liters or more may be present in cases of massive left auricular dilatation. Since the ether time is practically normal, there is no delay in the passage of the test substance from the arm vein through the right heart to the pulmonary capillaries. The prolongation of the circulation time is clearly in the circuit from the lungs to the end point. The most probable explanation is that the test substance, upon leaving the lungs, arrives at a large stagnant pool, the dilated left auricle. Here the material is greatly diluted and, presumably, poorly mixed. The blood ejected from the left ventricle contains the test substance in a highly diluted state. The prolonged circulation time may be explained by the long period necessary for the accumulation in the receptor organ of a sufficient concentration of the test substance to produce a detectable end point.

Several years ago Nylin,⁸ in a study of the residual blood of the heart, reported three patients with dilated hearts in whom the circulation time was prolonged. He suggested that the increased residual blood in the heart was the basis for the prolonged circulation time. Meneely and Kaltreider⁹ studied the blood volume, vital capacity of the lungs, venous pressure, circulation time, and other measurements in fifteen cardiac patients with congestive failure. They found no simple correlation between these various measurements. In eight patients, however, they noted a linear relationship between the logarithm of the circulation time and heart size as expressed by the ratio of the transverse cardiac diameter to the diameter of the chest. Aside from these references, apparently no consideration has been given to the possible role of cardiac enlargement in the prolongation of the circulation time.

METHODS AND MATERIAL

The purpose of the present study was to determine the influence of heart size on the circulation time in compensated cardiac patients. The group consisted of ambulant cardiac patients who required only slight or moderate restriction of physical activity. Using the classification suggested by the American Heart Association, most of the patients belonged either in Class I or Class II. Since the purpose of this study was to determine the influence of heart size on circulation time, the group consisted of patients showing varying degrees of cardiac enlargement. In addition to the routine physical examination, a tele-roentgenogram was made in each instance. The vital capacity of the lungs was measured in many of the patients. The circulation time was determined in most cases by the use of a solution described by Spier, Wright, and Saylor,¹⁰

which consists primarily of magnesium sulfate and calcium gluconate and is known as "macasol."* When injected in the arm vein, the arrival of the test substance in the throat is indicated by the abrupt development of a distinct sensation of warmth. The sensation then spreads to the hands, perineum, and lower extremities. In some instances the circulation time was checked also by the use of calcium gluconate or fluorescein. The average normal circulation time from arm to throat, using macasol, is 13.8 seconds. Variations within 25 per cent of the average value may be considered normal. For the estimation of heart size, the area of the frontal cardiac silhouette in the teleroentgenogram was utilized. This area was calculated by means of the formula $\pi/4$ long \times broad diameters.¹¹ According to Ungerleider and Gubner,¹¹ this method gives values which correspond closely to the area as obtained by planimetry. The calculation is simplified by the use of the nomograms of Ungerleider and Gubner. These nomograms give the predicted cardiac area from height and weight of the patient and the actual area as calculated from the long and broad diameters of the heart. The degree of cardiac enlargement was expressed by the ratio of the actual cardiac area to the predicted normal area.

It is realized that it would be more appropriate to estimate the size of the heart by the measurement of the cardiac volume rather than the cardiac area. We have utilized the area of the frontal silhouette for the following reasons: (1) there are technical difficulties in the measurement of the cardiac volume; (2) there is a reasonably close relationship between the area of the cardiac silhouette and the cardiac volume; and (3) the measurement of the frontal projection in the teleroentgenogram is the usual clinical method for the estimation of heart size.

RESULTS

The study includes seventy compensated cardiac patients with various types of cardiac pathology. The shortest circulation time was 9.4 seconds and the longest 62 seconds. Thirty-nine, or more than 50 per cent of the patients, had a circulation time of 20 seconds or more. The data are summarized in Tables I, II, and III, and in Fig. 2. Table II shows that there is a relationship between the

TABLE I. CIRCULATION TIMES IN SEVENTY COMPENSATED CARDIAC PATIENTS

CIRCULATION TIME (SECONDS)	NUMBER OF CASES
0 to 10	2
10 to 20	29
20 to 30	25
30 to 40	8
40 to 50	4
50 to 62	2

*Macasol contains 42 Gm. of magnesium sulfate, 16 Gm. of calcium gluconate, 0.9 Gm. of sodium chloride, and 1.0 mg. of copper sulfate in each 100 c.c. of distilled water.

TABLE II. HEART SIZE AND CIRCULATION TIMES IN SEVENTY COMPENSATED CARDIAC PATIENTS

{ HEART SIZE ACTUAL AREA PREDICTED AREA }	NUMBER OF CASES	CIRCULATION TIME (SECONDS)	
		RANGE	AVERAGE
1.0 to 1.5	24	9.5 to 41	19.4
1.5 to 2.0	33	10.3 to 50	22.8
2.0 to 2.5	10	13.9 to 41	26.9
2.5 to 3.0	3	15.0 to 62	34.3

degree of cardiac enlargement and the circulation time. There is a definite prolongation of the circulation time as the size of the heart increases. The data on heart size and circulation time are plotted on the graph in Fig. 2. The various types of cardiac pathology also are designated. The graph shows a considerable scatter in the values, but a statistically significant correlation between heart size and circulation time is demonstrated. The graph also reveals a tendency for the circulation times to be longer in mitral disease as compared with aortic insufficiency and hypertensive arteriosclerotic heart disease. This is further demonstrated in Table III, which shows that the mean circulation time in mitral disease is distinctly longer than in aortic insufficiency and hypertensive arteriosclerotic heart disease.

TABLE III. INFLUENCE OF TYPE OF CARDIAC LESION ON THE RELATIONSHIP BETWEEN HEART SIZE AND CIRCULATION TIME

LESION	NUMBER OF CASES	{ HEART SIZE ACTUAL AREA PREDICTED AREA }			CIRCULATION TIME (SECONDS)			
		MEAN	S. D.*	S. E.†	MEAN	S. D.	S. E.	"P" VALUE‡
Mitral	22	1.73	0.50	0.11	26.9	11.5	2.5	
Aortic	15	1.72	0.33	0.10	20.2	8.4	2.2	> 0.05
Mitral and aortic	11	1.73	0.22	0.07	24.8	12.9	3.9	> 0.6
Hypertension and arteriosclerosis	22	1.60	0.30	0.07	19.4	7.9	1.7	< 0.02

*Standard deviation of a single observation = $\sqrt{\frac{\sum d^2}{N-1}}$.

†Standard error of the mean = $\frac{S.D.}{\sqrt{N}}$.

‡Calculated according to Fisher, R. A.: Statistical Methods for Research Workers, Edinburgh, 1938, Oliver & Boyd, Ltd. The circulation time of the mitral lesion is compared with the other lesions. A "P" value of less than 0.05 indicates a significant difference between the means.

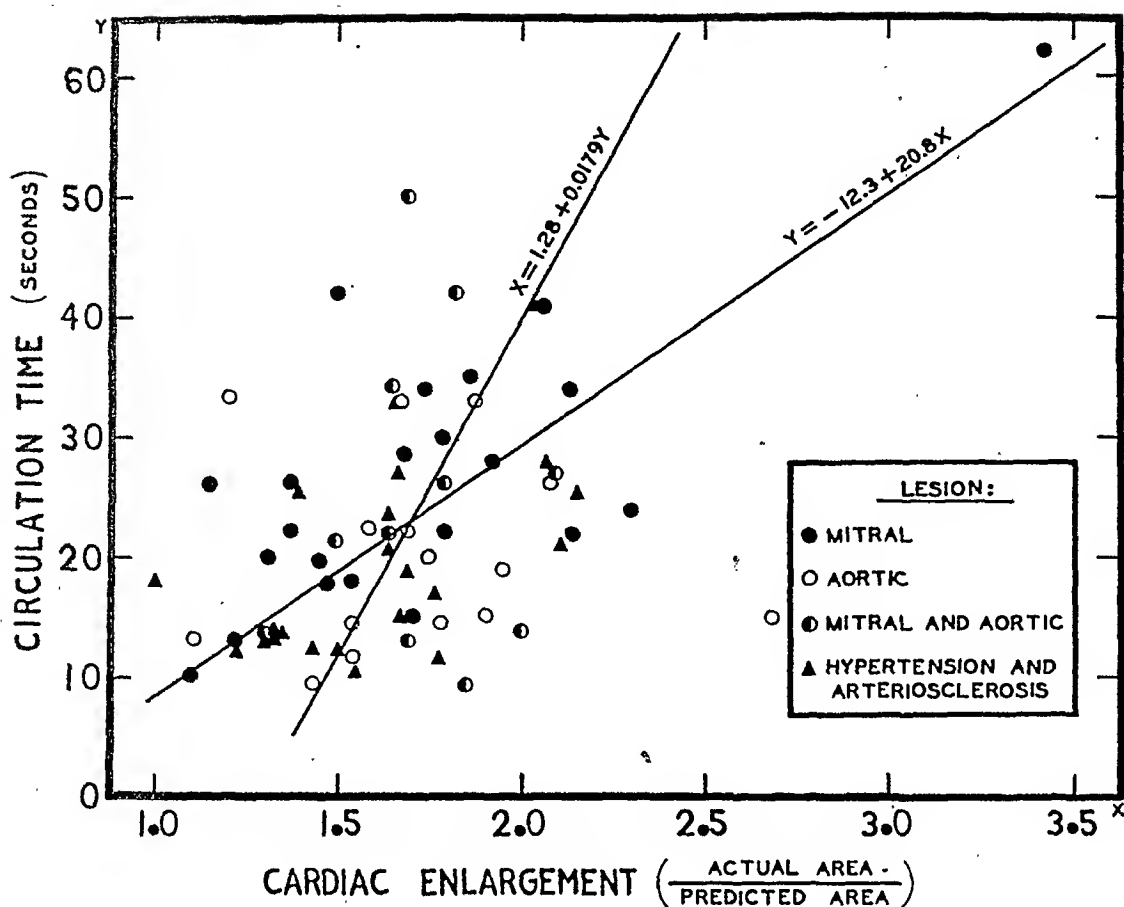


Fig. 2.—Graph showing the relationship between the heart size and circulation time in seventy patients with various types of cardiac pathology. In this graph the variables, cardiac enlargement ratio (X) and the circulation time (Y) were plotted and compared. Because the values seem to be widely scattered, regression lines were constructed, using each variable in turn as the independent and the dependent variable. The relationship between these variables was described and measured by least squares straight lines as follows: $Y = -12.3 + 20.8X$ and $X = 1.28 + 0.0179Y$. The scatter or standard error of the estimate of these lines was 8.64 seconds and 0.253 cardiac enlargement ratio. About 68 per cent of the circulation time values were in a normal distribution of ± 8.64 seconds. The coefficient of correlation was 0.610, and from this a "P" value of less than 0.001 was calculated. A "P" value of 0.001 indicates that the probability of a chance relationship between the two variables is only 1 in 1000. It follows that as the cardiac enlargement ratio increases, an increase occurs also in the circulation time.

The following are illustrative cases:

CASE 1.—T. A., a 37-year-old man, showed the characteristic signs of mitral stenosis. He was able to carry on his work as a radio engineer with slight limitation of activity. The lungs were clear; there was no enlargement of the liver. The vital capacity of the lungs was 3,600 c.c., which is within normal limits. The circulation time was 41 seconds. Fluoroscopic examination of the chest showed a markedly enlarged heart of mitral contour. In the right lateral position the barium-filled esophagus was compressed and displaced posteriorly beyond the anterior margin of the spine. The teleroentgenogram and right lateral view are shown in Fig. 3. The ratio of the area of the frontal silhouette to the predicted area was 2.05. This is an illustration of a markedly prolonged circulation time in a patient with mitral stenosis. This case should be compared with Case 2 in which a fairly normal circulation time is associated with a comparable degree of cardiac enlargement in a patient with aortic insufficiency.



Fig. 3.—Patient T. A. Teleroentgenogram and right lateral view with barium-filled esophagus showing marked dilatation of the left auricle in a patient with mitral stenosis. The circulation time was 41 seconds. The cardiac enlargement ratio was 2.05.

CASE 2.—M. K., a 31-year-old man, presented the typical signs of aortic insufficiency. There was no evidence of congestive failure. The vital capacity of the lungs was 3,800 c.c., which is within normal limits. The circulation time was 19 seconds. Fluoroscopic examination of the chest showed a markedly enlarged heart of the left ventricular type. The pulsations of the left ventricle were very forceful. The barium-filled esophagus showed no evidence of left auricular dilatation. The teleroentgenogram is shown in Fig. 4. The ratio of the actual cardiac area to the predicted area was 1.95. This case illustrates a fairly normal circulation time associated with considerable enlargement of the heart in a patient with aortic insufficiency.



Fig. 4.—Patient M. K. Teleroentgenogram showing left ventricular dilatation in a patient with aortic regurgitation. The circulation time was 19 seconds. The cardiac enlargement ratio was 1.95.

CASE 3.—I. R., a 54-year-old man, gave a history of a coronary occlusion in January, 1945. When seen on Aug. 3, 1945, he stated that he had no complaints and that he carried on his activities as a business executive without discomfort. There was no objective evidence of passive congestion. The vital capacity of the lungs was 3,000 cubic centimeters. The circulation time was 27 seconds. A teleroentgenogram showed definite cardiac enlargement, the ratio of actual area to predicted area being 1.86 (Fig. 5). From January, 1946, to March, 1946, there was increasing dyspnea on moderate effort. On March 19, 1946, there were a few râles at the lung bases and the vital capacity was reduced to 2,000 cubic centimeters. The circulation time was 26.6 seconds. The findings in this patient are of interest for they indicate that in some instances the predominant factor in the prolongation of the circulation time is the cardiac dilatation and in this circumstance the development of a mild degree of cardiac decompensation may have no further appreciable effect on the circulation time.

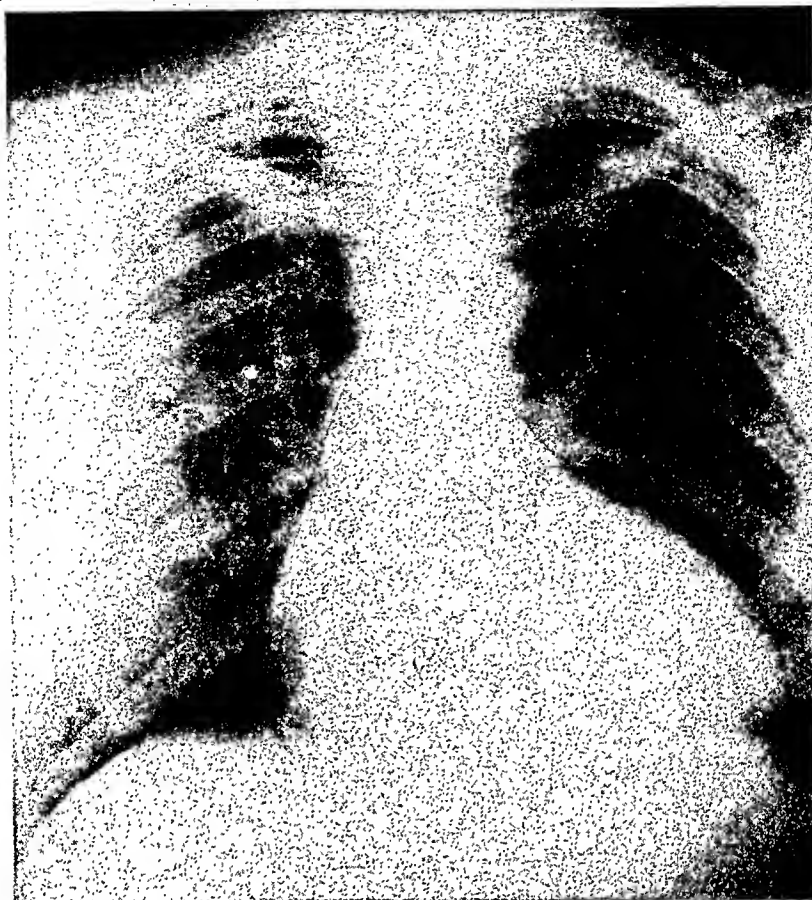


Fig. 5.—Patient I. R. Teleroentgenogram of patient with coronary disease. There was no evidence of cardiac decompensation. The circulation time was 27 seconds.

DISCUSSION

It is evident that a prolonged circulation time occurs in patients with cardiac enlargement in the absence of symptoms and signs of congestive failure. Furthermore, there is a correlation between the magnitude of the cardiac dilatation and the increase in the circulation time. In consideration of the mechanism by which a dilated heart may influence the circulation time, it should be pointed out that the clinical measurement of circulation time includes two components: (1) the true physiologic circulation time, that is, the time required for the fastest particle of the test substance to traverse the shortest path between the point of injection and the place of detection, and (2) the time required for the accumulation in the receptor organ of a concentration of the test substance necessary for detection. These two components may be influenced in a dilated heart. The heart and blood vessels form a closed system of tubes and the velocity of flow of a liquid in such a system varies inversely as the square of the radius. Since the cross-sectional area of the flowing stream is increased, it is clear that the actual velocity of flow (the velocity of the fastest particle) is reduced in a dilated heart and that the circulation time is prolonged. Cardiac enlargement also provides conditions which delay the accumulation in the receptor organ of a detectable concentration of the test substance. The test substance entering a dilated cardiac chamber becomes abnormally diluted in the increased volume of blood. Also,

in a dilated heart, the stroke output is relatively small as compared with the large content of residual blood, and this may lead to a slow and incomplete mixing of the test substance in the intracardiac blood. Thus the blood ejected from a dilated heart chamber contains the test material in a diluted and incompletely mixed state. The level of the test substance rises slowly in the peripheral blood and there is a delay in the accumulation of a detectable concentration in the receptor organ. Nylin¹² studied the concentration in the arterial blood of intravenously injected red blood cells labeled with radioactive phosphorus. In individuals with enlarged hearts there was a delayed appearance of the labeled cells in the peripheral blood, and the rise in concentration was gradual as compared with the early appearance and abrupt rise in normal individuals.

The influence of the type of lesion on the relationship between heart size and circulation time is of interest. Two explanations for the relatively longer circulation time in mitral disease may be considered. First, the area of the frontal silhouette may give an inadequate measurement of the cardiac volume in mitral disease as compared with lesions which predominantly affect the left ventricle, such as aortic regurgitation and hypertensive heart disease. In mitral disease a considerable volume of the residual blood is in the dilated left auricle and this chamber is not at all or only partially visualized in the frontal projection. Thus the longer circulation time in the mitral heart may be consistent merely with a cardiac volume which is incompletely expressed by the area of the frontal silhouette. Second, there is the possible difference in the reaction of the test substance in the mitral heart as compared with the heart of aortic insufficiency or hypertension. The pulsations of the dilated left auricle in mitral disease are wavelike and of small amplitude. This may effect a relatively slow and incomplete mixing of the test substance in the intra-auricular blood. In aortic insufficiency and hypertension, the increased residual blood is chiefly in the left ventricle. The contractions of this chamber are active and forceful, favoring a rapid and complete mixing of the test substance. In Nylin's study¹² on the dilution curves following the injection of labeled red blood cells, there was one exceptional case in which the heart was considerably enlarged and yet the rise in the level of the tagged cells was rapid and abrupt, similar to the response in hearts of normal size. It is of interest that the diagnosis in this case was aortic regurgitation.

The demonstration of the influence of the intracardiac blood on the circulation time modifies some of the accepted interpretations of circulation time measurements. Blumgart¹ studied the circulation time from the arm to the right heart and from the right heart to the periphery. He considered that the time of flow from the right heart to the periphery was a measure of the velocity in the pulmonary circulation since most of this time is spent in the flow through the lesser circulation. He disregarded the time of flow through the heart, indicating that this interval is very short. Although this is true in the normal heart, the present studies show that a dilated heart can participate substantially in the prolongation of the "pulmonary" circulation time. It is apparent that the use of the "pulmonary circulation time" as an index of the velocity of blood flow through

the pulmonary circulation would lead to an incorrect interpretation of circulatory measurements.

It is clear that an increase in the amount of blood interposed between the site of injection of the test substance and the point of detection will prolong the circulation time. In the arm-to-head segment, the increased volume involves chiefly the intrathoracic blood which includes the content of the heart and the content of the pulmonary vessels. In cardiac disease, the increased blood volume may be limited to the heart or it may include both the heart and pulmonary vessels. The intracardiac blood content may be greatly increased without affecting the clinical condition of the patient, but an increase of the volume in the pulmonary circulation (pulmonary congestion) results in dyspnea, orthopnea, and cough. Thus the following combinations may occur: (1) a pro-

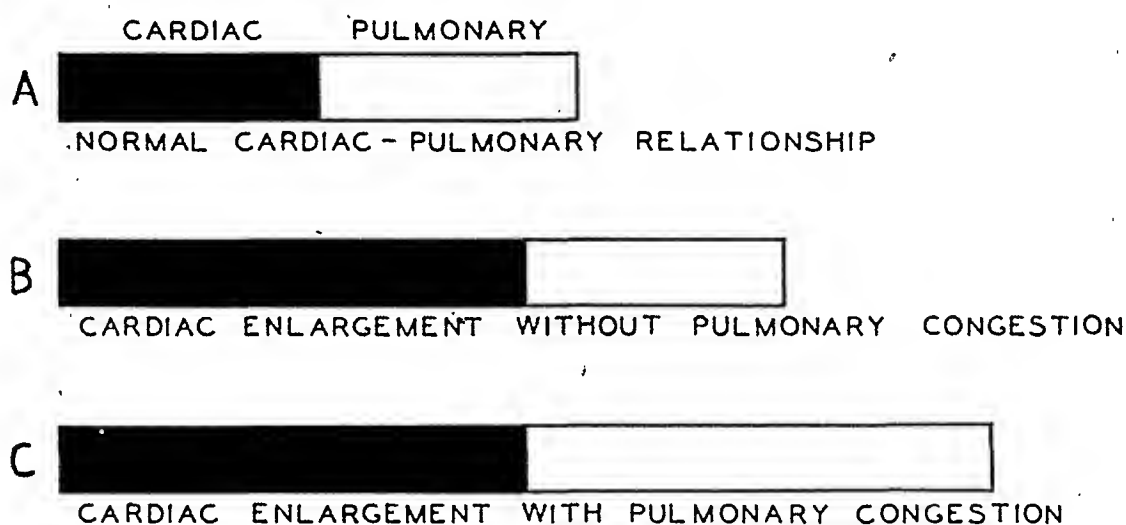


Fig. 6.—Diagram showing the influence of the distribution of the intrathoracic blood in determining the relationship between the circulation time and the clinical condition of the patient. A, Circulation time normal, congestive failure absent. B, Circulation time prolonged, congestive failure absent. C, Circulation time prolonged, congestive failure present.

longed circulation time with no evidence of congestive failure, in which situation the increased blood volume is limited to the heart, and (2) a prolonged circulation time associated with congestive failure, in which the increased blood volume includes both the heart and the pulmonary circulation. This is shown diagrammatically in Fig. 6. In evaluating the significance of a prolonged circulation time it is evident that the influence of cardiac dilatation must be taken into account. The recognition of the cardiac factor provides a broader and more accurate interpretation of circulation time measurements.

CONCLUSIONS

1. In seventy compensated cardiac patients with cardiac enlargement, the circulation time was longer than 20 seconds in more than 50 per cent.
2. There was a rough correlation between the degree of cardiac enlargement and the circulation time.

3. With a comparable degree of cardiac enlargement there was a relatively longer circulation time in patients with mitral disease than in patients with aortic regurgitation and hypertensive arteriosclerotic heart disease.

4. A prolonged circulation time does not necessarily signify an actual reduction in the velocity of blood flow but may be due entirely to an improper mixing and a dilution of the test substance in the increased residual blood of a dilated heart.

5. The relationship between the circulation time and the clinical condition of the patient depends on the manner of distribution of the intrathoracic blood.

ADDENDUM

Since this paper was submitted for publication, the following report has been published by Gernandt, B., and Nylin, G.: The Relation Between Circulation Time and the Amount of the Residual Blood of the Heart, *AM. HEART J.* 32:411, 1946. This report clearly demonstrates a significant correlation between the heart volume and the circulation time in both compensated and decompensated heart disease.

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A PRELIMINARY STUDY OF THE CORONARY CIRCULATION POST MORTEM

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THE purpose of this preliminary report is to emphasize the need for a rapid, complete, and objective method of routinely studying the coronary circulation post mortem and to present a technique which meets these needs.

As to the need, Karsner⁷ says, "Of the various diseases [of the heart] which are of importance, arteriosclerosis of the coronary arteries, because of the frequency in those periods of mature life when the integrity of bodily function serves in a large sense the welfare of mankind, deserves most intimate study." And yet, accumulations of accurate objective data on coronary disease are relatively scanty.

Rapidity of Technique.—A rapid technique is desirable so that the clinician may be presented, within a reasonable length of time (approximately one to one and one-half hours after the heart has been removed), not only the gross pathologic changes in the three layers of the myocardium and in the cardiac valves, but also a complete two-dimensional visualization of the entire coronary circulation by means of a wet roentgenogram.

Completeness of Technique.—The technique must offer a complete injection of the arterial system as far as precapillary arterioles. It should also lend itself readily to a systematic clinicopathologic study of diseases of the heart in general and specifically those of the coronary arteries.

Possible Lines of Investigation.—A complete injection technique suggests certain lines of investigation.

Correlation of Cardiac Arrhythmias With Disturbances in Circulation: Gross and associates^{4,5} described a distinct and specific blood supply for the principal segments of the conduction system and found that morphologic disturbances of the system could be correlated with functional derangements. These significant observations require further study (Fig. 1).

Correlation of Atrial Infarcts With Circulatory Disturbances: Since the report of Wartman, Feil, Cushing, and Stanton²⁵ recognition of atrial infarcts has become more widespread, yet the etiology has remained obscure. By injection and

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radiographic visualization of the coronary tree, the demonstration of the presence or absence of occlusions in atrial branches, or in the parent artery proximal to their origin, may help to clarify the cause of atrial infarcts.

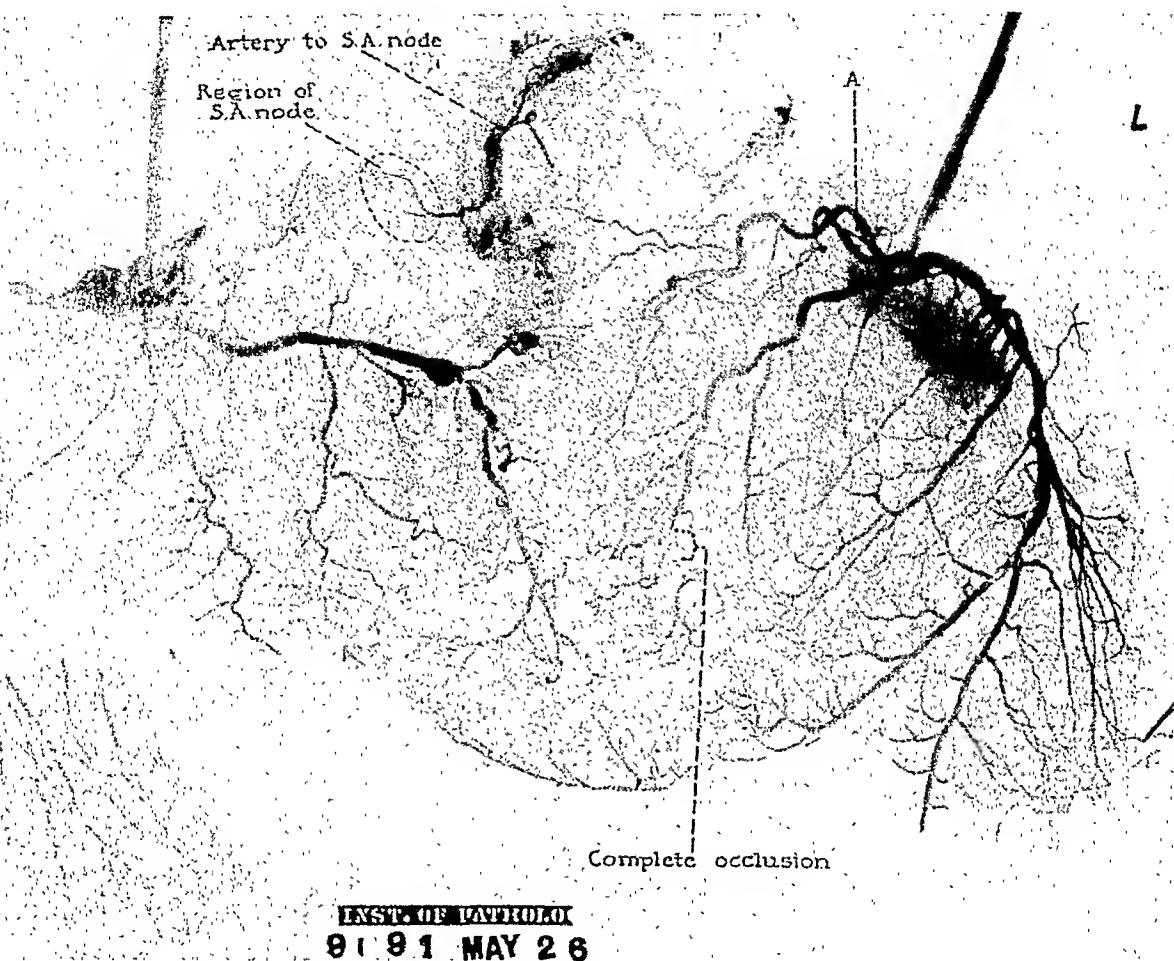


Fig. 1.—This 69-year-old white woman has had electrocardiographic changes of "left typical bundle branch block" for approximately two and one-half years. At autopsy an organizing complete occlusion was demonstrated in the distal radicals of the marginal branch of the circumflex ramus of the left coronary artery. Moderate endocardial sclerosis was diffusely demonstrable over the left ventricular portion of the Interventricular septum.

Growth of Coronary Circulation: Some authors maintain that a pattern of growth is responsible for the relevant changes that occur in the coronary arteries, usually in middle life. Others conclude that regardless of the ontogenetic process, "the event which precipitates occlusion of a coronary artery is not referable to the history of the artery, but to an accident, morphologic, metabolic, immunological, or bacteriological."² A routine standardized method of visualization of the coronary arteries from infancy to old age might shed some light on these fundamental concepts.

Genetic Aspects of Coronary Circulation: Schlesinger^{18,19} has found after, studying 269 hearts, that the coronary artery pattern is not exactly the same in any two human hearts and that these multitudinous variations can be classified into three distinct anatomic patterns, each differing in its vulnerability to arte-

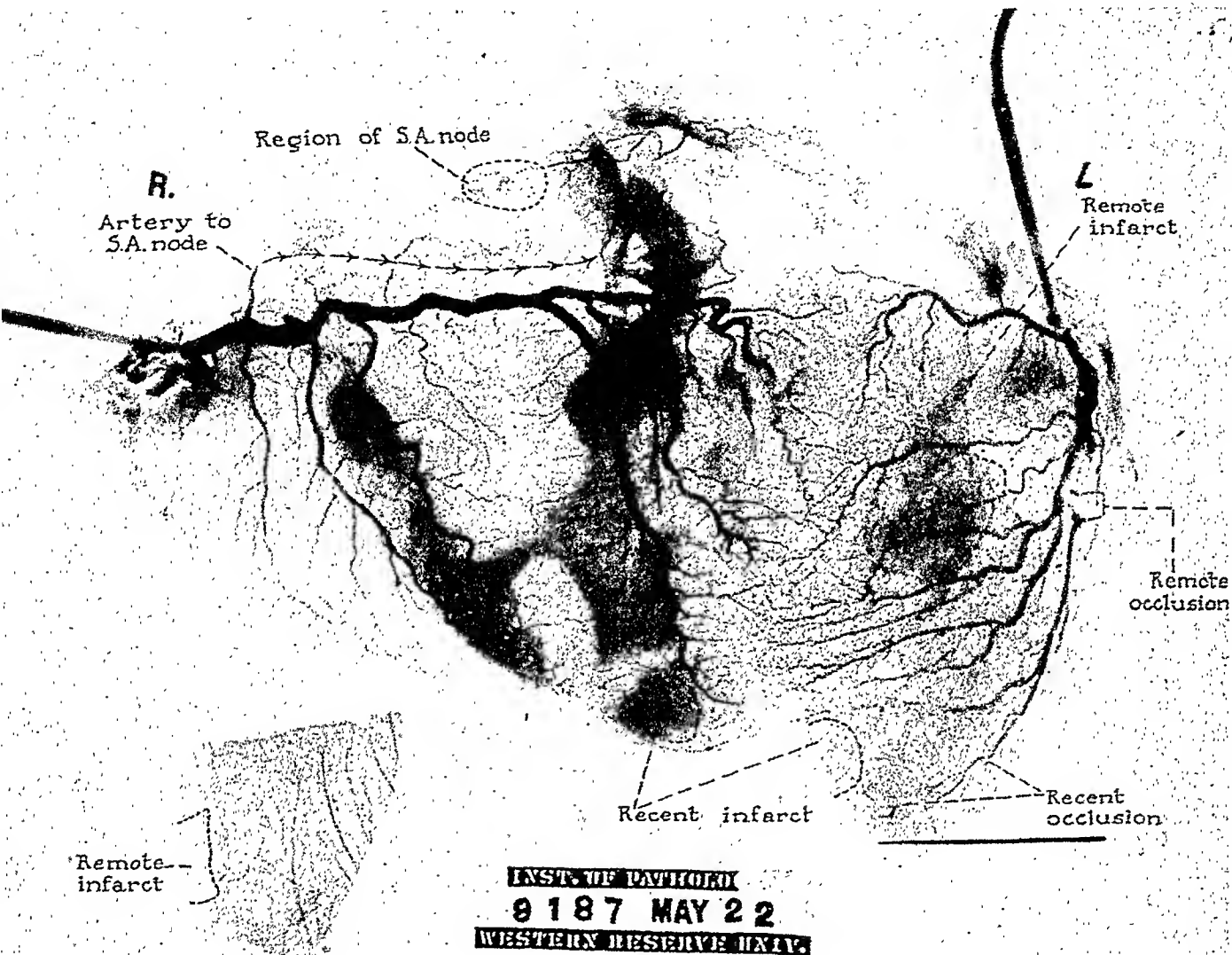


Fig. 2.—This 52-year-old white man with diabetes died from carcinoma of the right lung with metastases to the liver. Acute bacterial endocarditis of noncoronary cusp of the aortic valve was discovered at autopsy, with occlusion of a small terminal radical of the descending ramus of the left ventricle, measuring 1.4 by 1.8 by 1 centimeter. A remote occlusion of the descending ramus of the left coronary artery approximately 3 cm. from the origin and extending .7 cm. was located. An electrocardiogram taken approximately one month before death was reported as a normal record. Note this is a 2 plus right preponderant coronary artery pattern.

riosclerosis (see Fig. 2). With these observations he concludes that the well-known familial tendency to coronary artery disease may be a function of inherited patterns of the coronary arteries. He also feels that correlation of electrocardiograms with these patterns may be possible. Objective records of the coronary arterial circulation, routinely gathered from autopsies, would serve to confirm or negate these interesting speculations.

Deep Divisions of the Coronary Arteries: Wearn and collaborators²⁶⁻³⁰ found, "That finer divisions of the coronary arteries present a far more complex picture [than the larger vessels] the knowledge of which is still incomplete and in some cases controversial." Whitten and Barnes,³² after studying these finer branches, have attached significance to the angle at which, from the exterior, a coronary artery branch penetrates the substance of the cardiac muscle. The necessity of a medium which will consistently penetrate these fine channels and lend itself to corrosion with the production of nonfriable, nonbrittle, elastic casts becomes evident for a comprehensive clinicopathologic correlation of the deep circulation of the heart. It follows also that with increasing skill in the surgical treatment of coronary disease and with the ultimate death of patients so treated, the pathologist must be equipped to evaluate objectively the extent of surgically created collaterals.



Fig. 3.—Vascularity in the posterior leaflet of the mitral valve injected with red with the medium from the left coronary artery.

Vascularity of Valves: For the demonstration of vascularity in the heart valves post mortem, there is probably no substitute for the microscope.⁸ However, it is certain that the routine sections may occasionally by-pass the region of vascularity. A method of directing attention to these regions, as by a colored radiopaque injection mass, is desirable for a more complete correlation of the minimal valvular lesions, so frequently seen at the autopsy table, and of the other established stigmas of rheumatic fever, such as Aschoff nodules and endocardial reduplication of valves (see Fig. 3).

Muscle Bundle Concept of Cardiac Pathology: Based on the earlier studies of MacCallum¹⁰ and Mall¹¹ on the demonstration of distinct muscle bundles in the human heart, Robb and co-workers¹²⁻¹⁷ have presented some novel concepts with important potentialities. These observations have not been fully confirmed, but only because there has been little investigation along these lines. A technique of complete arterial injection with the formation of a solid flexible cast would lend itself readily to further correlation of muscle bundle patterns with coronary artery patterns.

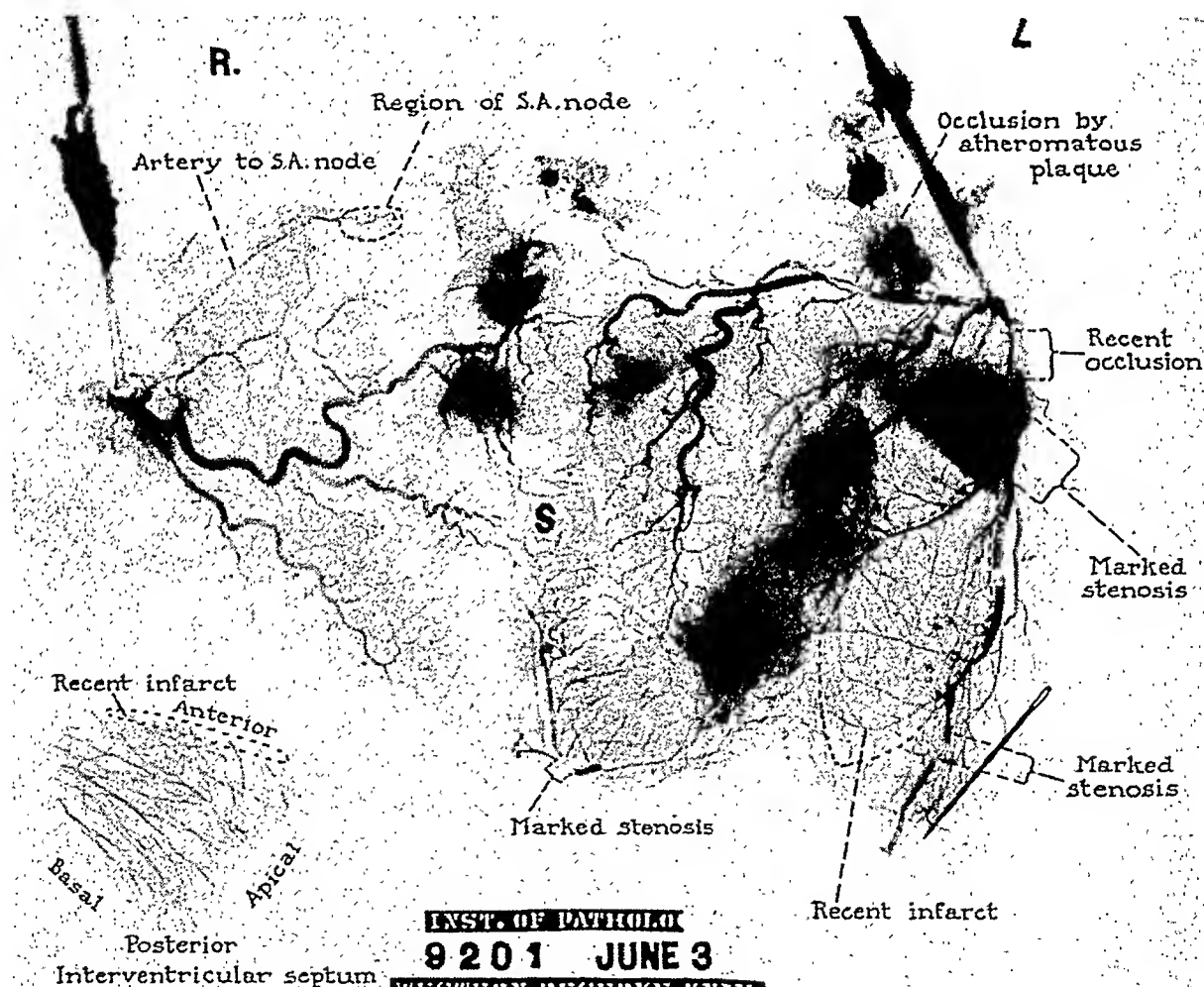


Fig. 4.—Approximately 80 per cent of the arterial system was injected with the blue medium from the right coronary artery, including most of the vessels seen within the area of recent infarct and more than 90 per cent of the interventricular septum. No established arrhythmias were noted clinically. (Note the artery to the sinoauricular node arises from the nonoccluded right coronary artery.) S indicates the area of enucleated septum. The patient died in heart failure approximately four days after clinical manifestations of acute myocardial infarct.

Prognosis of Coronary Disease: Fifty per cent of all men over fifty years of age studied by Schlesinger¹⁹ revealed at least one occlusion somewhere in the coronary arterial system. It would seem, therefore, that any statistical data as to the incidence or prognosis of coronary disease would have to include occlusions and, as will probably follow, infarcts that have hitherto gone unrecognized by the routine manual method of dissection of the coronary tree (see Fig. 4).

Objectiveness.—A fundamental postulate for accurate inference from mass data is that the records which compose the data be assembled by objective standardized methods. Notoriously inadequate are descriptions of the coronary arterial system which speak of minimal and moderate sclerosis, stenosis, etc. Similarly inadequate are descriptions of infarcts as anterior or posterior, basal, or apical. The following is a description of a technique, aided by illustrations (Figs. 5 and 6), which can be routinely employed in the study of the coronary arteries post mortem, without the sacrifice of other pathologic entities, and which will lend itself readily to a study of the problems mentioned.

HISTORICAL DATA

The literature discloses many and diverse methods for demonstration of the vascular system of the human body. All of these have been applied in one way or another to the study of the coronary arteries. The first method was simple dissection, which von Haller²⁴ used in 1757 to give the first detailed knowledge of the blood supply to the heart. A systematic study of this field, even today, cannot be had without the aid of dissection. Certain plans have, however, greatly facilitated this long and, of necessity, incomplete procedure.

The earliest investigators injected dyes, and in some cases silver nitrate, for the purpose of recognizing the blood vessels in both gross and microscopic preparations. Swammerdam,²² in 1672, was the first to inject a substance which would harden in the coarser vessels. This medium, hot wax mixed with oil and fats and stained with cinnabar, was used almost exclusively throughout the eighteenth century. Additional methods have been adequately reviewed in the classical monographs of Spalteholz,²¹ Gross,⁴ and Whitten.³¹

A recent significant contribution was that of Schlesinger,¹⁹ who devised a technique of unrolling the heart, so that the entire arterial system could be laid out on one plane, strikingly resembling the Spalteholz diagram. Schlesinger's technique with the use of a lead phosphate agar mass was employed in a total of twenty-seven hearts. However, it was necessary to abandon the use of his medium for the following reasons: (1) A great deal of time was consumed in the preparation of the medium and it was found to be unstable when prepared; (2) the mass was not fine enough to penetrate the small vessels consistently; (3) it was found to be inadvisable to suspend the heart in warm saline (44°C.) for twenty minutes or longer; (4) it was not possible to prepare corrosion specimens; (5) it was not possible to prevent leakage from the small vessels adequately while injecting.

In 1937 Hill⁶ suggested the use of latex rubber in various anatomic procedures. Batson,¹ Gamble,³ and Tobin²³ have used this compound to advantage, and Lieb²

has developed a technique for the use of Neoprene, a synthetic latex, in adequately demonstrating the vascular bed of the human kidney. Most of her work was done with corrosion specimens, and the technique, because of the time consumed before demonstration, does not lend itself to a routine practical study of the coronary circulation. Recently, Smith and Henry²⁰ have used Lieb's technique in injecting the dog heart.

Neoprene, although less desirable than latex, because of its slowness of gelation in cold temperatures and its greater instability when employed with barium sulfate, may, however, be adapted to the following technique.

TECHNIQUE

Apparatus.—The apparatus consists of a mercury constant pressure trap which is connected to an air pressure line. The desired constant pressure may be obtained by raising or lowering the inner tube. A Wolff bottle serves as a reservoir for this air pressure and a mercury manometer has been utilized so that the pressure in the apparatus may be accurately gauged. A liter bottle is used for the saline and the latex bottles have a capacity of 100 cubic centimeters. These bottles have been graduated so that the amount of latex which fills each coronary artery can be measured. The rubber tubing connections should be as short as possible, for it is difficult to clean all of the latex out of the tubes. If, however, the tubes are thoroughly rinsed immediately after use, they may be used again, three or four times. The vacuum jar (Fig. 5) may be obtained commercially.*

Cannulation.—The right and left coronary arteries are dissected free as they originate from the aorta, and two-inch glass cannulae are securely fastened into the arteries, as close to the origin of the vessels as possible, with 40-gauge cotton suture. (A bowknot facilitates the removal of the cannulae after injection has been completed.)

The cannulae are prepared from glass tubing (3/16 inch with 1/16 inch bore). The tube may be drawn out to any desired bore, and with intravenous needles varying from 18 to 25 gauge the cannulae are flanged in the following manner: the needle is coated with talcum powder and heated until the head becomes red hot. By quickly inserting the needle into the cannula and exerting pressure against the needle, the desired flange will be produced (Fig. 6). It has been found that a cannula with a short blunt head will make possible injection of vessels which arise close to the origin of the coronary arteries.

Washing.—After the cannulation the heart is washed with a total of approximately 500 c.c. of physiologic saline at room temperature. The washing is done separately for each coronary artery and is completed when the return flow from the opposite coronary artery is clear. Simultaneous washing of the coronary arteries was abandoned after the suggestion of Lieb,⁹ that interstitial edema might occlude the smaller rami of the arterial tree and thus prevent a complete injection. The swelling of the heart was noted to be significantly less with the independent washing of each vessel.

*Sold under the name of Jumbo Vacuum Jar Number 820 by the American Thermos Bottle Co., Norwich, Conn.

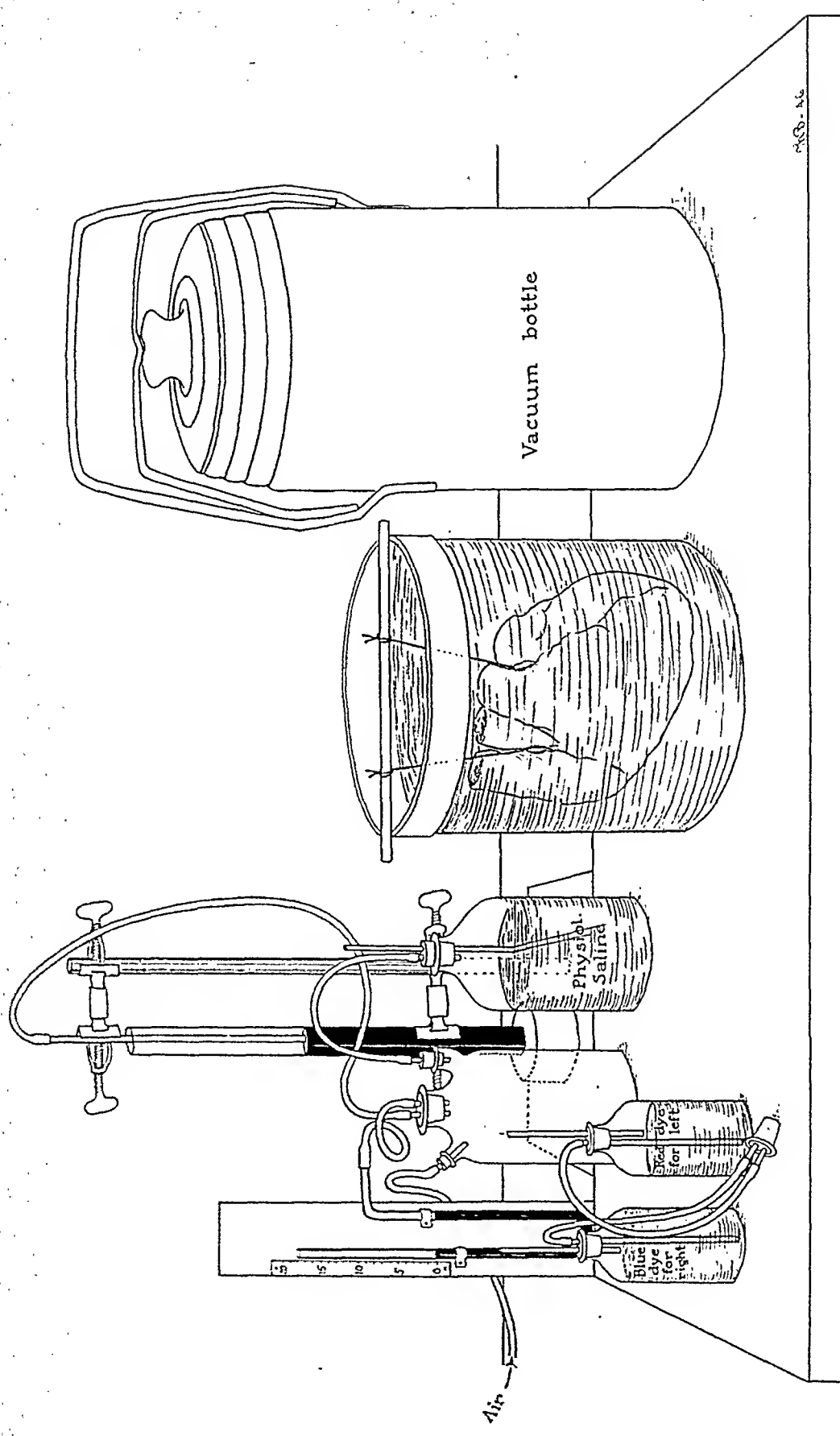


Fig. 5.—Diagram showing apparatus described in text.

Injection.—A suspension of barium sulfate in an aqueous ammoniated solution of latex rubber is employed.† Compound No. 60-22724 A (red) and 60-22724 B (blue) was selected because it provides maximum radiopacity with consistent injection of precapillary arterioles of 15 to 25 micra in luminal diameter. A 2 per cent aqueous solution of ammonium hydroxide may be used to dilute the compound to a viscosity approaching that of water, at the expense, however, of diminishing radiopacity. The medium is prepared with red and blue organic dyes (injected into the left and right coronary arteries respectively) which do not bleach with the subsequent treatment. When the union of red and blue material occurs, as with intercoronary anastomoses, the colors are maintained and the vessels appear streaked with red and blue.

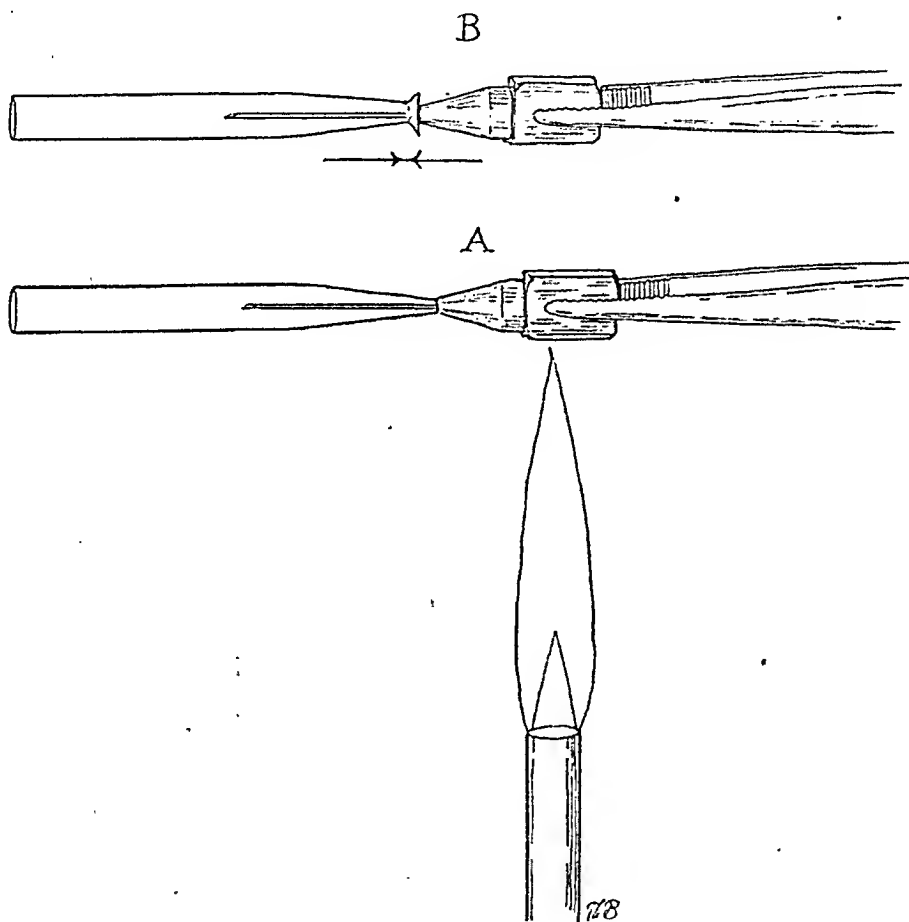


Fig. 6.—A illustrates the heating of the needle while inserted in the glass tubing. B illustrates the resulting flange when pressure is exerted with the hot needle.

Pressure is allowed to build up in the apparatus until the desired level is reached before the clamps on the tubes leading to the cannulae are released. This permits maximal pressure to be released and the vessels to be injected simultaneously. Originally an effort was made to simulate the ante-mortem pressure. Consistently good results, however, were obtained with pressures of 150 mm. Hg for adult hearts and 100 mm. for hearts weighing 150 grams and less.

The heart is suspended during injection in a solution of 2 per cent glacial acetic acid and 4 per cent formaldehyde in 70 per cent ethyl alcohol, which

†Obtained from American Anode Company, Akron, Ohio.

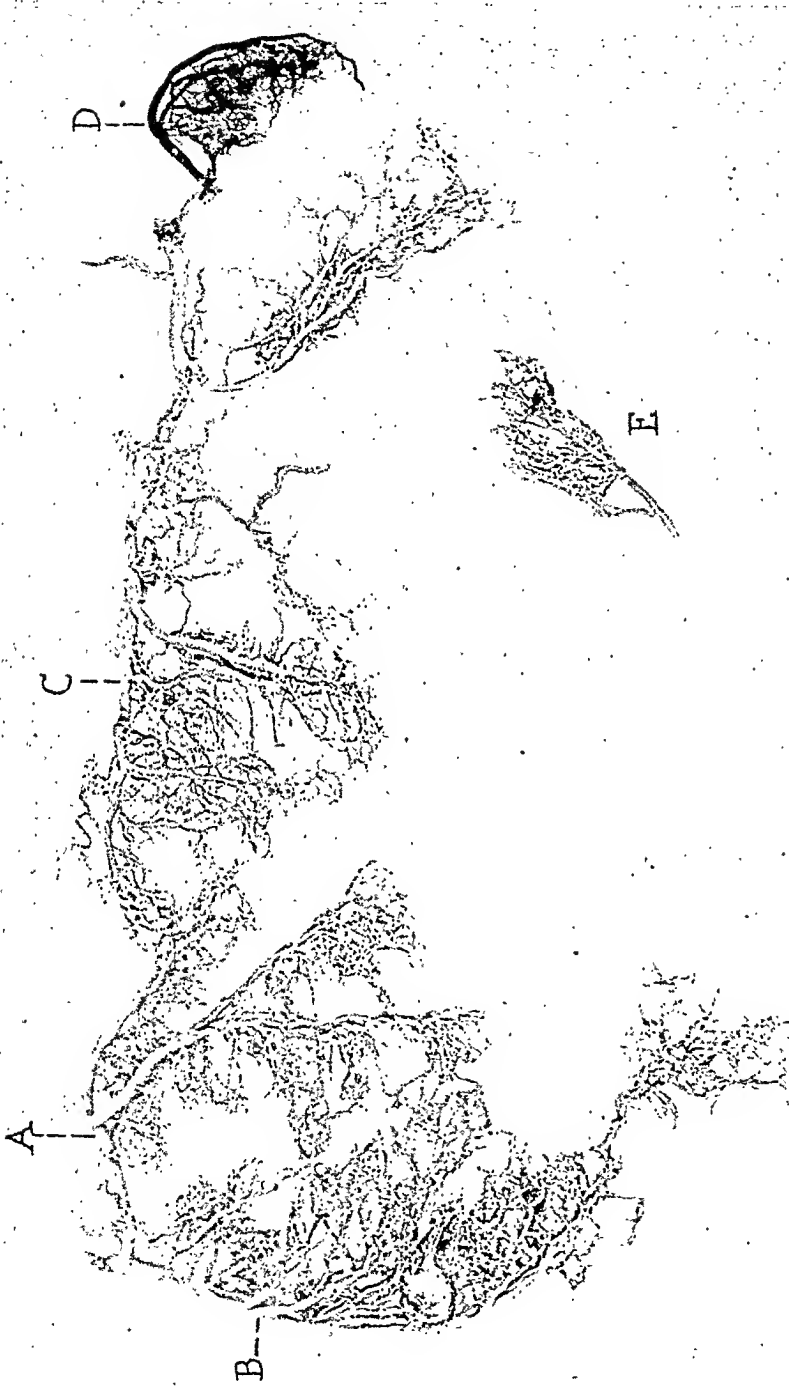


Fig. 7.—Corrosion specimen of the normal heart with injection of right accessory coronary ostium and the cast of its circulation, *D*. *A*, Circumflex ramus of the left coronary artery. *B*, Descending ramus of the left coronary artery. *C*, Main right coronary artery. *D*, Accessory right coronary artery. *E*, Interventricular septum (more than 80 per cent of the vessels injected from the left coronary artery).

promptly coagulates the compound as it escapes from the minute vessels severed in the process of removing the heart. Injection is completed in from five to fifteen minutes, depending upon the size of the heart. The pressure is maintained in the vessels after injection by means of bulldog clamps placed on the rubber tubes leading to the cannulae. The heart is then placed in a vacuum bottle containing a 95 per cent alcoholic solution of 2 per cent glacial acetic acid and 4 per cent formaldehyde at a temperature of -13°C . (kept constant with cracked ice). There it remains for from twenty to forty minutes, the time again varying with the size of the heart, or until the organ is in a firm but not frozen state. In the event that this low temperature plus acidification does not gel the compound completely, pledgets of cotton soaked in 4 per cent glacial acetic acid should be on hand to minimize leakage during the unrolling of the heart. The unrolling procedure is carried out exactly as advocated by Schlesinger.

Roentgenography.—Following the unrolling, the heart is x-rayed, employing the following technique: kilovolt peak, 38; milliamperes, 10; distance, 36 inches; time, 10 seconds; medium cone. An opaque marker is placed in the region of the enucleated septum, with orientating markers to designate the right and left coronary arteries. The technique is so standardized that a technician can demonstrate the wet roentgenogram approximately one to one and one-half hours after the heart has been removed.

The cannulae are then removed and the injected specimen is fixed in a 4 per cent formaldehyde solution acidified with 2 per cent glacial acetic acid. Dissection of large nonoccluded vessels at the autopsy table is not advisable because the gelling may be reversible; however, if corrosion specimens are not desired, then leakage is of no consequence and random dissection may be carried out immediately.

Corrosion specimens are adequately prepared (after fixation) by macerating the muscle tissue in concentrated hydrochloric acid (commercial) (see Fig. 7). If this is done at 56°C . in an incubator, the process may be completed in from twelve to eighteen hours. If it is desirable to clear the specimens, caution should be taken not to use rubber solvents such as xylol and benzene.

During histologic preparation, "tearing" of the section may occur when large vessels are encountered. This may be minimized by icing the block and by cutting the sections at 8 to 10 micra. Microscopic detail is well preserved.

The x-ray negatives or prints of these negatives may be incorporated into the protocol, thus providing permanent objective data for further comprehensive study.

RESULTS

To date ten hearts have been injected with the technique described. Frozen sections cut at 12 to 16 micra have revealed consistent injection of precapillary arterioles (15 to 25 micra in luminal diameter) regardless of the time post mortem. One heart was considered inadequately injected when the cannula leading to the left coronary artery became plugged with debris from improperly cleaned tubing. Injection of the posterior leaflet of the mitral valve occurred in a heart which was

the seat of moderate aortic stenosis (Fig. 4). An instructive corrosion specimen was prepared from one injected heart (Fig. 5) with the demonstration of the circulation from the cannulated accessory right coronary ostium.

SUMMARY

The need for an objective, rapid, and complete method of routinely studying the coronary arterial circulation post mortem is presented with suggestive lines of investigation. A technique so qualified which combines natural latex as injection compound with Schlesinger's method of unrolling the heart is described. A method of cooling is described which facilitates the setting of the injection mass. A method of preparing cannulae is also given.

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FURTHER OBSERVATIONS ON THE TREATMENT OF THE ANGINAL SYNDROME WITH THIOURACIL

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RAAB¹ and Ben-Asher,² in 1945, reported on the observation, made independently, that thiouracil is effective in the treatment of the anginal syndrome. Of the ten patients with angina pectoris treated with the drug, Raab found that seven showed clinical improvement. In the eight patients that the author treated, the results obtained were excellent in two, good in five, and fair in one.

The explanation for the beneficial results obtained with thiouracil in angina pectoris is probably the same as for total thyroidectomy. Levine and Eppinger³ believe that thyroidectomy results in an alteration in the sensitivity of the heart to adrenalin. These authors found that the rise in blood pressure and pulse rate, induced by the intramuscular injection of adrenalin, was greatly diminished when the test was performed after total thyroidectomy. They also have shown that in patients in whom adrenalin produced an attack of angina pectoris the injection did not cause an attack after the operation. They, therefore, conclude that the improvement following thyroidectomy may be brought about by the diminished sensitivity of the heart to adrenalin, as well as by the decrease in the work of the heart resulting from a fall in the basal metabolic rate. As further evidence to support this theory, Raab⁴ found that thyroxin sensitizes the heart in the rat to epinephrine and that pretreatment with thiouracil reduces the sensitivity.

Shambaugh and Cutler⁵ suggest that the therapeutic results of thyroidectomy in angina pectoris may be due to an interference with the thyro-adrenal mechanism. Anginal pains are frequently associated with a rise in blood pressure and pulse rate caused by a sudden increase in the secretory activity of the adrenals. The beneficial results of thyroidectomy, they suggest, may be due to a diminished effectiveness of the physiologic output of adrenalin.

The advantage of reducing the function of the thyroid with a drug rather than by a radical surgical procedure is obvious. It is the purpose of this paper to present the results of treatment with thiouracil in twenty-nine additional patients with angina pectoris as well as to report on a follow-up of the patients described in the first report.²

From the cardiac clinics of the Medical Center and the Greenville Hospital, Jersey City, N. J.
The thiouracil was supplied by Dr. Stanton M. Hardy of the Lederle Laboratories, Inc., Pearl River, N. Y.

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MATERIAL AND METHOD

Twenty-nine patients, twenty-four men and five women, with angina pectoris were studied at the cardiac clinics of the Jersey City Medical Center and the Greenville Hospital. This makes a total of thirty-seven patients thus far treated with thiouracil. The ages varied from 42 to 69 years. All had had angina pectoris for a period of time, varying from eight months to nine years. Thirteen patients had a history of an old coronary occlusion.

Each patient had a complete history, physical examination, blood count, and basal metabolism test before treatment was begun. In some patients blood cholesterol determinations were made before and during treatment. All of them were observed for one to two months before treatment. Blood counts were made once or twice weekly for the first two months and later were made at longer intervals.

The patients were divided into two groups. In one (Group A), studied in the early period of this investigation, twenty patients received an initial daily dose of 0.6 Gm. of thiouracil by mouth until clinical improvement was noted. This dose was given for two to three weeks, after which the patients were placed on a daily maintenance dose of 0.1 to 0.2 Gm. for a period varying from three to seven months. In the second group (Group B), the initial daily dose was 0.4 Gm. followed by a maintenance dose of 0.1 to 0.2 Gram.

In order to eliminate the possibility of suggestion, twelve patients received a placebo in the course of this study. This consisted of tablets which looked like thiouracil in size and shape. In eight patients the course of treatment was interrupted by the placebo for periods of two to eight weeks. Four patients received the placebo at the completion of treatment for periods of six weeks to four months.

The patients were instructed to continue their previous activities, if possible, and to report at each visit (1) the number of anginal attacks experienced, (2) the severity and duration of each attack, (3) the amount of physical activity before the attack occurred, and (4) the number of nitroglycerine tablets used since the last visit.

In order to obtain objective data, standardized exercise tolerance tests, as described by Master,⁶ were performed on ten patients before treatment and at frequent intervals during the investigation. This consisted of ascending and descending a two-step staircase and noting the number of ascents necessary to induce substernal or precordial discomfort. Each test was made at least two hours after a light meal. The room temperature was kept between 72° and 76°F.

The results were classified as excellent, good, fair, and poor according to the criteria which follow. The results were regarded as *excellent* if (1) the patient did not experience any precordial distress in the course of normal activities, (2) there was an increase of 100 per cent or more in the exercise tolerance test. The results were regarded as *good* if (1) mild pain occurred infrequently, (2) there was an increase of at least 100 per cent in physical activities, (3) there was an increase of at least 50 per cent in the exercise tolerance test. The results were regarded as *fair* if (1) there was an increase of 50 per cent in the normal physical

TABLE I. RESULTS IN TWENTY PATIENTS (GROUP A) WITH ANGINA PECTORIS TREATED WITH AN INITIAL DAILY DOSE OF 0.6 Gm. OF THIOURACIL

CASE	NAME	AGE	SEX	DURATION OF ANGINA PECTORIS	DEGREE OF ANGINA PECTORIS	BLOOD PRESSURE	B. M. R.		ONSET OF IMPROVE- MENT (WK.)	DURATION OF TREAT- MENT	RESULTS	DURATION OF IM- PROVEMENT AFTER DRUG WAS STOPPED (MO.)	REMARKS
							BEFORE THIOURACIL THERAPY	MAXIMUM CHANGE UNDER TREATMENT					
1	F. M.	54	F	5 yr.	4+	160/100	+24	-12	2	5 mo.	Good	9	Relapse eight mo. after drug was stopped; response to a second course of 0.4 Gm.
2	C. J.	46	M	2 yr.	2+	146/80	+6	-18	3	5 mo.	Good	10	Relapse under 2 mo. of placebo given at completion of treatment; response to second course of 0.4 Gm.
3	C. R.	62	M	16 mo.	4+	130/70	+14	-16	4	5 mo.	Excellent	16	Improvement maintained to date
4	R. D.	52	M	9 mo.	3+	160/110	+12	-8	3	5 mo.	Good	8	Relapse 5 mo. after drug was stopped; response to a second course of 0.4 Gm.
5	P. S.	48	M	1 yr.	4+	176/100	+8	-20	6	4 mo.	Good	11	Relapse under 6 wk. of placebo given at completion of treatment; response to a second course of 0.4 Gm.
6	C. S.	46	M	15 mo.	4+	120/70	+4	-16	4	5 mo.	Good	15	Improvement maintained to date
7	G. T.	62	M	8 yr.	4+	200/120	+16	-12	6	6 mo.	Fair	15	No change in status under 2 mo. of placebo given at completion of treatment
8	C. R.	47	M	16 mo.	3+	126/70	-6	-18	4	18 wk.	Good	14	Improvement maintained to date

9	S. A.	69	M	1 yr.	3+	218/110	+18	—	—	2 days	Poor	—	Thiouracil stopped on third day because of fever
10	H. D.	44	M	6 yr.	2+	120/80	+11	-27	1	7 mo.	Excellent	7	Relapse when course was interrupted by 3 wk. of placebo
11	B. P.	43	M	30 mo.	4+	146/80	+10	-15	—	6 mo.	Poor	—	Symptoms of myxedema; status unchanged with treatment
12	C. E.	54	M	2 yr.	3+	160/90	+6	—	—	1 wk.	Poor	—	Died of coronary occlusion in second week of treatment
13	F. N.	66	F	1 yr.	2+	190/110	-4	-13	2	7 mo.	Good	5	Relapse when course was interrupted by 6 wk. of placebo
14	J. M.	44	M	20 mo.	3+	120/80	+12	-24	2	6 mo.	Excellent	7	Symptom free; increase in number of ascents 155%
15	F. Y.	57	M	9 yr.	4+	160/96	+16	—	—	9 days	Poor	—	Thiouracil stopped on tenth day because of fever
16	M. C.	48	M	30 mo.	3+	140/80	+8	-20	3	13 wk.	Fair	8	Thiouracil stopped in fourteenth week because of neutropenia
17	F. P.	64	M	2 yr.	4+	230/120	+12	-28	—	6 mo.	Poor	—	Status unchanged with treatment
18	W. R.	58	M	15 mo.	4+	120/80	+21	—	—	2 days	Poor	—	Thiouracil stopped on third day because of fever
19	S. J.	42	M	4 yr.	3+	140/76	+16	-18	1	6 mo.	Excellent	5	Improvement maintained to date
20	M. M.	66	M	2 yr.	2+	180/100	+14	-6	2	3 mo.	Good	6	Thiouracil stopped in thirteenth week of treatment because of neutropenia

The first eight cases were described in a previous paper.

TABLE II. RESULTS IN SEVENTEEN PATIENTS (GROUP B) WITH ANGINA PECTORIS TREATED WITH AN INITIAL DAILY DOSE OF 0.4 GM. OF THIOURACIL

CASE	NAME	AGE	SEX	DURATION OF ANGINA PECTORIS	DEGREE OF ANGINA PECTORIS	BLOOD PRESSURE	B. M. R.		ONSET OF IMPROVE- MENT (WK.)	DURATION OF TREAT- MENT	RESULTS	DURATION OF IM- PROVEMENT AFTER DRUG WAS STOPPED (MO.)	REMARKS
							BEFORE THIOURACIL THERAPY	MAXIMUM CHANGE UNDER TREATMENT					
21	G. L.	60	M	3 yr.	2+	130/86	+12	-13	3	7 mo.	Good	6	Relapse when course was interrupted by 4 wk. of placebo
22	F. P.	45	F	8 mo.	2+	146/90	+8	-26	2	6 mo.	Excellent	5	Symptom free; increase of 118% in number of ascents
23	J. C.	57	M	2 yr.	4+	220/140	-7	—	—	6 mo.	Poor	—	Status unchanged with treatment
24	M. L.	50	F	18 mo.	3+	176/100	+14	+2	6	5 mo.	Fair	4	Status unchanged under 4 mo. of placebo given at completion of treatment
25	T. P.	61	M	2 yr.	3+	160/110	+39	—	—	6 days	Poor	—	Thiouracil stopped on seventh day because of fever
26	L. G.	44	M	9 mo.	4+	129/76	-5	-20	5	6 mo.	Good	4	Symptom free; increase in number of ascents only 71%
27	C. T.	62	M	1 yr.	4+	166/90	+12	-4	—	6 mo.	Poor	—	Status unchanged with treatment

28	E. C.	47	M	6 yr.	3+	140/80	+6	-26	3	7 mo.	Excellent	3	Relapse when course was interrupted by 3 wk. of placebo
29	H. R.	63	F	20 mo.	2+	200/100	-2	-18	3	6 mo.	Good	2	Relapse when drug was interrupted by 2 wk. of placebo
30	M. R.	59	M	10 mo.	3+	146/90	+8	-20	6	6 mo.	Fair	2	Status unchanged when course was interrupted by 2 mo. of placebo
31	J. N.	52	M	4 yr.	3+	150/86	-6	-24	—	6 mo.	Poor	—	Status unchanged with treatment
32	S. R.	43	M	15 mo.	4+	130/70	+16	-8	3	6 mo.	Excellent	3	Symptom free; exercise tolerance test increased 132%
33	H. G.	48	M	1 yr.	3+	186/70	+7	-27	5	7 mo.	Good	2	Relapse when course was interrupted by 4 wk. of placebo
34	L. C.	58	M	18 mo.	4+	216/120	+10	-14	—	6 mo.	Poor	—	Symptoms of myxedema; status unchanged with treatment
35	S. L.	44	F	16 mo.	3+	140/76	-4	-12	4	15 wk.	Fair	3	Thiouracil stopped in sixteenth week because of neutropenia
36	E. P.	49	M	3 yr.	3+	160/90	+24	+8	3	7 mo.	Good	2	Relapse when course was interrupted by 6 wk. of placebo
37	M. H.	60	M	2 yr.	4+	206/112	+9	—	—	4 days	Poor	—	Thiouracil stopped on fifth day because of fever

activity before the occurrence of pain, (2) there was an increase of 25 per cent in the exercise tolerance test. The results were regarded as *poor* when these criteria were not met.

RESULTS

Results Based on Subjective Response.—In Table I is shown the result of treatment of twenty patients with angina pectoris with an initial daily dose of 0.6 Gm. of thiouracil. Definite clinical improvement was obtained in fourteen patients (70 per cent). In these fourteen patients, the results were excellent in four, good in eight, and fair in two. The onset of improvement occurred within one to six weeks. The average was three weeks. The average duration of treatment was 5.2 months. Improvement has been maintained for five to sixteen months after thiouracil was discontinued. Four of five patients in this group had relapses when placed on a placebo. In two the relapses occurred when the course of treatment was interrupted by a placebo, and two had relapses when placed on a placebo at the completion of treatment. In one the status remained unchanged when the placebo was administered at the end of treatment. The four who had relapses responded to a second course of 0.4 Gm. of thiouracil as an initial dose.

In one patient (Case 20) the drug was stopped in the thirteenth week and in another (Case 16) in the fourteenth week of treatment because of neutropenia.

Of the five patients in whom the results were classified as poor, the drug was discontinued in two on the third day and in one on the tenth day because they developed fever. One patient who had evidence of an old myocardial infarction died of a coronary occlusion in the second week of treatment.

Of the eight patients described in a previous report relapses occurred in two patients. In one patient (Case 1) the relapse occurred eight months after the drug was discontinued and in the second (Case 4) five months after cessation of treatment. Both responded to a second course consisting of 0.4 Gm. of thiouracil as an initial dose. The result in Case 1, previously regarded as excellent, is now regarded as good.

Table II gives the result of treatment in seventeen patients who received an initial dose of 0.4 Gm. of thiouracil. These patients were studied in the later period of this investigation. Clinical improvement was evident in eleven patients (64 per cent). Of these eleven, the results were excellent in three, good in five, and fair in three. The onset of improvement occurred within two to six weeks. The average was 3.9 weeks. The average duration of treatment was 5.9 months. In these, improvement has been maintained for two to six months after the drug was discontinued. Relapses occurred in five of seven patients who were placed on a placebo. In these five, the relapse occurred when the course of treatment was interrupted by the placebo. Of the two in whom the status remained unchanged, one received the placebo during the course of treatment and the other received it at the end of treatment. The five patients who had relapses responded to a second course of thiouracil.

In two patients in this group the drug was stopped because of a fever. In one (Case 37) the fever occurred on the fifth day, and in the second (Case 25) on the seventh day of treatment. In one patient (Case 35) thiouracil was discontinued in the sixteenth week of treatment because of the development of neutropenia.

Improvement has been maintained for from three to six months in the three patients in both groups who developed neutropenia in the fourth month of treatment. The results in both groups thus treated were excellent in seven, good in thirteen, fair in five, and poor in twelve.

Results Obtained with the Standardized Exercise Tolerance Test.—Table III shows the results of this test before treatment and at the time of maximum improvement with thiouracil. In three patients there was an increase of more than 100 per cent in the number of ascents, in five patients the increase was more than 50 per cent, in one patient it was more than 25 per cent, and in two patients it was less than 25 per cent. In one patient (Case 26) who was symptom free under normal activities the increase in the number of ascents was only 71 per cent.

TABLE III. RESULTS WITH STANDARDIZED EXERCISE TOLERANCE TEST

CASE	AVERAGE NUMBER OF ASCENTS		INCREASE (PER CENT)
	BEFORE TREATMENT	AT TIME OF MAXIMUM IMPROVEMENT	
11	15	18	20
13	17	25	64
14	20	51	155
16	18	24	33
20	24	41	79
21	28	47	60
22	21	49	133
26	14	24	71
32	16	39	132
34	13	15	15
36	18	31	72

Changes in the Basal Metabolic Rate.—Before treatment the basal metabolic rate varied from -7 to $+39$ per cent. With thiouracil therapy the range was between $+8$ and -28 per cent.

In ten patients of Group A and in seven of Group B the basal metabolic rate was less than -15 per cent. Although there was generally a reduction in the basal metabolic rate with thiouracil treatment, the fall did not always correspond with the clinical result. In one patient (Case 17) in whom the result was classified as poor, the basal metabolic rate before treatment was $+12$ per cent; under thiouracil the basal metabolic rate fell to -28 per cent. In another patient (Case 32) in whom the result was classified as excellent, the basal metabolic rate before treatment was $+16$ per cent, and at the time of maximum improvement it was only -8 per cent.

Changes in the Blood Cholesterol.—Determinations of the blood cholesterol were made on ten patients. The results are shown in Table IV. Before treatment the blood cholesterol varied from 174 to 216 mg. per cent. The average was 197 mg. per cent. With thiouracil, the range was between 224 and 446 mg. per cent. The average was 278.6 mg. per cent. Here also the rise in blood cholesterol did not always correspond with the clinical result. In Case 19, in which the result was classified as excellent, there was an increase of 50 mg. per cent. In Case 34, in which the increase in blood cholesterol was equivalent to 252 mg. per cent, and in which symptoms of myxedema developed, the clinical response was poor.

TABLE IV. EFFECT OF THIOURACIL TREATMENT ON BLOOD CHOLESTEROL

CASE	BLOOD CHOLESTEROL (MG. PER CENT)	
	BEFORE TREATMENT	MAXIMUM CHANGE WITH TREATMENT
10	196	272
13	210	258
19	174	224
21	182	230
26	208	274
29	190	262
30	216	288
32	188	238
34	194	446
35	212	294

Effect on the Electrocardiogram.—A diminution of 2 mm. in T_1 was noted in five patients. In nine patients T_1 and T_2 were lowered 1 millimeter. An elevation of 2 mm. in T_1 and of 3 mm. in T_4 occurred in three patients. The typical low voltage of the QRS complexes described in myxedema was not noted.

Effect on Weight and Blood Pressure.—An average increase of 6 pounds in weight was noted in eighteen patients under thiouracil therapy. This increase occurred largely in the third month of treatment. No appreciable effect on the blood pressure was noted.

Reaction to Thiouracil.—Toxic effects were noted in eight patients treated with thiouracil. Of these, five patients developed fever. In Group A, two patients had a fever on the third day and one patient on the tenth day of treatment. In Group B, one patient had fever on the fifth day and another on the seventh day of treatment. The temperature became normal when the drug was discontinued. Neutropenia was noted in three patients. In Group A, one patient developed neutropenia in the thirteenth week and another in the fourteenth week of thiouracil therapy. One patient in Group B developed neutropenia in the sixteenth week of treatment. The white count returned to normal spontaneously when the drug was stopped.

COMMENT

These studies which have extended over a period of thirty-two months confirm the observation that thiouracil is effective in the treatment of the anginal syndrome. The fact that relapses occurred in nine of the twelve patients placed on a placebo, as well as the results obtained from the standardized exercise tolerance test, eliminate the possibility of suggestion as a factor in the therapeutic response.

The danger of toxic reactions is, however, a definite drawback in the use of the drug in angina pectoris, as it is in hyperthyroidism. In this series, fever and neutropenia were the only ill effects noted. Agranulocytosis, a more serious reaction reported in the literature, was not encountered. Although encouraging results have recently been obtained in treating this reaction with penicillin,⁷⁻⁹ all patients receiving thiouracil should be carefully observed, particularly with reference to the blood.

One must also consider the ill effects of hypercholesterolemia on the coronary arteries resulting from the thiouracil therapy. Further studies are necessary to determine the role of cholesterol in the pathogenesis of arteriosclerosis.

SUMMARY AND CONCLUSIONS

1. Thiouracil was found to be beneficial in twenty-five of thirty-seven patients (67 per cent) with the anginal syndrome.
2. Definite improvement was obtained in fourteen of twenty patients (70 per cent) receiving an initial daily dose of 0.6 Gm. of thiouracil. The onset of improvement began, on the average, after three weeks of treatment.
3. Eleven of seventeen patients (64 per cent) improved with an initial daily dose of 0.4 Gm. of thiouracil. The onset of improvement averaged 3.9 weeks.
4. Five patients developed fever in the first ten days of treatment.
5. Three patients developed neutropenia in the fourth month of treatment.
6. Thiouracil is an effective drug in the treatment of angina pectoris. The smaller dose (0.4 Gm.) is almost as effective as the larger dose (0.6 Gm.). Toxic reactions may occur with both.

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RAYNAUD'S DISEASE IN MEN

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THE vasospastic disorders are a group of peripheral vascular disturbances in which the arterial circulation is impaired, either intermittently and spasmodically or more or less continuously, as a result of tonic contractions of blood vessels. They are differentiated from the obliterative arterial diseases by the general absence of pathologic changes in the walls of the arteries, leading to narrowing or occlusion of the lumen, except in those instances in which the process is long continued or very severe.

Of the group of vasospastic conditions, the clinical entity which is best known was first described by Raynaud^{1a} in 1862 and has since been designated by his name. In the interval a great number of reports have appeared in the literature indicating a wide divergence of opinion as to what criteria are necessary for the diagnosis of Raynaud's disease. Some workers have grouped together loosely a variety of circulatory disorders in which there is present as a common feature an abnormal responsiveness to cold. Others have attempted to limit the term Raynaud's disease rigidly to a progressive disorder without preceding local injury or disease which possesses the following characteristics: it occurs primarily in women, with onset in the second or third decade, and is typified by intermittent episodes of symmetrical blanching or cyanosis of the fingers and toes, and occasionally of the tips of the nose and ears, as a result of exposure to cold or emotional excitation. A popular concept has arisen that a triphasic color reaction is an essential component of Raynaud's disease; namely, blanching, followed by cyanosis, and then rubor as the attack passes away. Beginning with Raynaud¹ himself, however, numerous students²⁻⁵ of this malady have recognized that the initial color change may be either pallor or cyanosis.

Since a typical color response to cold or emotion may also occur as part of the clinical picture of a variety of conditions, it has been suggested that all patients showing this type of response as a secondary manifestation should be classified under Raynaud's syndrome or phenomenon. The term Raynaud's disease should then be reserved for those cases in which no etiology can be dis-

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covered and which have showed intermittent episodes of digital syncope or cyanosis for a relatively long period of time (at least two years) without the appearance of any signs of occlusive arterial disease.⁶

The present report deals with an analysis of fifty cases of Raynaud's disease in men, as studied in a Center set up by the Army for the care of patients with vascular disorders. For the most part, the clinical stories of the individuals in the group conform to the rigid criteria previously enumerated, except that in approximately one-half of the patients the condition had existed for less than two years at the time of their hospitalization. Not included in the series are all instances of Raynaud's syndrome observed in men in whom frostbite, local trauma, or the use of vibrating tools appeared to be the causative factor; these cases were otherwise identical in symptomatology and physical findings. Those patients who demonstrated typical manifestations but in whom there was the slightest suspicion that organic vascular disease was the basis for these responses were likewise omitted from the group.

Since most observers have reported that primary Raynaud's disease occurs almost exclusively in women, a general feeling has arisen that the disorder is extremely rare in men and that such a diagnosis is very likely to be in error. The purpose of this study, therefore, is to emphasize the recent observation of Hines and Christensen,⁷ that typical Raynaud's disease does exist in men as well as in women and, in addition, to point out that the types of cases observed under the stress and strain of Army life are no different from those seen in civil life.

CLINICAL RESULTS

In every patient in the series, either the color change had been noted by the attending medical officer during the present hospitalization or in previous medical installations, or the occurrence of this phenomenon was so regular and so clear cut that its existence could be established through interrogation. Four of the group were Negroes; the remaining forty-six patients were white. The age of the patients ranged from 21 to 51 years, the average age being 29.5 years. In twenty the disorder was of one year's duration or less, in six it had been present from one and one-half to two years, and in the remaining twenty-four it had existed for from two to thirteen years. In the great majority of patients the first attack occurred during cold weather; in a few it appeared in cool weather. Many of the patients were either civilians at the time or were in the Army but were still in the United States. In only one patient did the symptoms first arise either immediately before or during conditions of combat. The critical temperature subsequently necessary to initiate an attack varied widely, some patients undergoing blanching in slightly cool weather, others only during severe cold. Immersion of limbs in cold water or even ice water was much less effective in eliciting the response than was exposure of the body to a low environmental temperature. In fourteen patients some neuropsychiatric background or emotional instability was found, but in only one of these were the attacks of digital pallor brought on

by emotion. Of the remaining thirty-six patients, in whom no psychiatric stigmas were observed, this stimulus was effective, nevertheless, in producing the typical color changes in four.

Twenty-five of the fifty patients studied showed all the features which have been considered classical. On exposure to cold, the involved digits would turn dead white and the patient would have a feeling of intense coldness, numbness, and stiffness. Generally a clear-cut line of demarcation was present between the portion of the digit showing the pallor and that manifesting a normal color of the skin. On exposure to a warm environment, the digits would become cyanotic after a varying interval, rubor would follow, and then the normal color would return. In the later stage of the attack most of the patients would complain of tingling, throbbing, burning, or other paresthesias.

In the remaining twenty-five patients in this group the triphasic color reaction was not present. In nine cyanosis alone followed the blanching, with a subsequent return to normal color, ten showed rubor immediately after the pallor but with no intervening noticeable cyanosis, four demonstrated the blanching alone, followed directly by return of normal color, one demonstrated cyanosis and then restitution of normal color, and one demonstrated cyanosis followed by rubor without pallor. In all instances, however, the initial response was either pallor or cyanosis, pallor being much more frequent.

Syncope involved varying segments and numbers of digits. In some patients only the tips of the fingers or toes were affected; in others the change occurred either in the distal phalanx, the distal two phalanges, or in the entire digit. All four extremities were involved in five patients, both hands and one foot in two, both hands in thirty-five, one hand in five, one hand and both feet in one, the two feet in one, and one foot in one patient.

Asymmetrical distribution of the color changes in the two limbs was noted in twelve patients. Of this number, six exhibited pallor in one or several digits of a single extremity only, while in six there was asymmetry of involvement of the two paired limbs. In the remaining thirty-eight patients symmetrical changes were noted. In three of these, all ten digits of the hands and feet were involved; in four, all fingers of the two hands; in fourteen, the second, third, fourth, and fifth fingers of the two hands; and in one, all ten toes. It must be pointed out that in a number of the patients demonstrating symmetrical involvement, the history revealed that first one or two digits in a single extremity showed the change and that subsequently there was a progressive spread to other portions of the hand or foot and eventually to the contralateral limb.

The presence of symptoms was not always coincident with the actual occurrence of blanching. In fact, a number of patients had experienced numbness, coldness, stiffness, and paresthesias in the involved limbs years before the onset of the episodes of color changes. In some, although the symptoms were generally worse on the side exhibiting the attacks of pallor or cyanosis, exposure to cold frequently elicited similar complaints in the contralateral limb, in which color changes did not occur.

In the interval between attacks many of the patients were asymptomatic and maintained a normal circulation. However, about one-half of them dem-

onstrated some evidence of excessive sympathetic activity. This manifested itself as either cool, moist, and slightly cyanotic hands or feet or only coolness and excessive sweating. In some instances, moderate hyperhidrosis was noted without any alteration in cutaneous temperature or skin color.

Trophic changes occurred in eight patients. Generally they were slight and consisted only of some distortion of the nails or minimal thickening of the skin. However, in some the skin covering the finger tips seemed actually to be separated from the deeper tissues, and pressure applied to it would produce a temporary dimpling (Fig. 1). One patient demonstrated bilateral gangrene of the finger tips of a limited extent (Fig. 2,4). It is of interest that in two patients trophic changes occurred very early in the disease. One of these deserves further men-

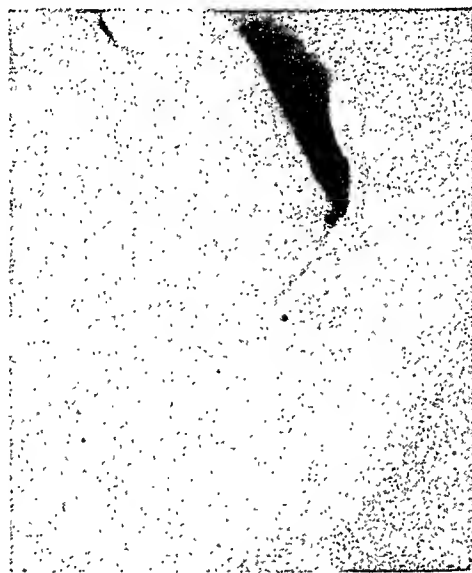


Fig. 1.—Fairly recent case of Raynaud's disease, showing dimpling of skin of tip of thumb after application of pressure. Phenomenon is due to loss of subcutaneous tissue.

tion. This individual was a 21-year-old man without previous vascular manifestations who had developed sensitivity to cold only three weeks before admission. While exposing his hands to a low external environment, he observed the right second, fourth, and fifth fingers to become very cyanotic, intensely cold, and uncomfortable. When he returned indoors the hand became warm and some time later the cyanosis and discomfort disappeared. Thereafter coldness, blueness, and some numbness of the fingers of both hands occurred on exposure to cold, with discomfort limited to the right hand. When examined upon admission, the hands were found to be cool and moist and the finger tips, with the exception of the thumbs, already showed thickening of the skin and striking loss of subcutaneous pulp, so that the skin dimpled upon pressure. This change was more obvious in the right index finger, which was the digit most sensitive to cold. Exposure of the hands to a low environmental temperature brought about intense cyanosis of the fingers.

Examination of the peripheral circulation in a warm environment consistently revealed no abnormalities in any of the patients in the group. All the pulses were readily palpable in the extremities, except for the occasional absence of the

dorsalis pedis pulse on one or both sides. No signs of arteriosclerosis were noted. Similarly, the various simple procedures for the determination of the state of the circulation, such as the plantar pallor test, the venous filling time, oscillometry, and the production of local vasodilatation through body heating or paravertebral sympathetic block with procaine, all indicated that no organic vascular disease existed.

A.

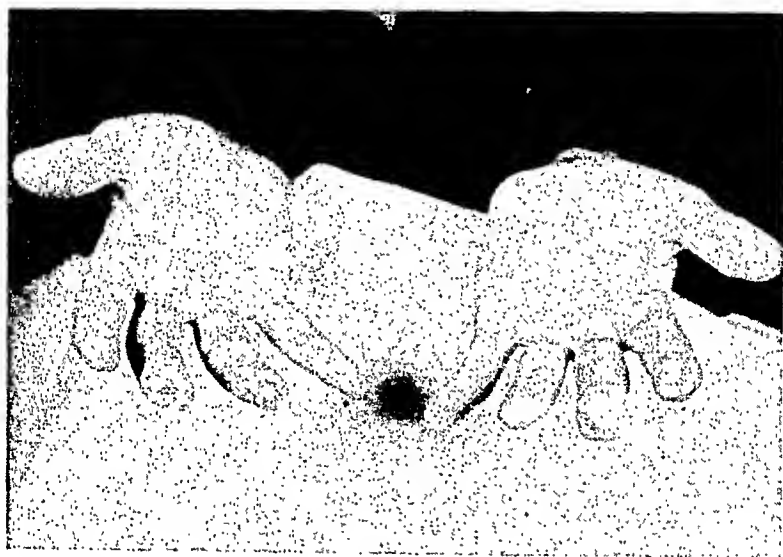
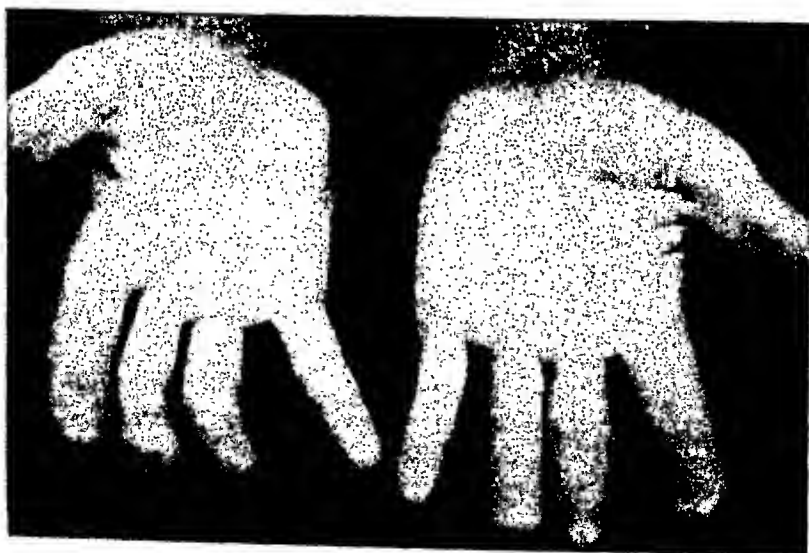


Fig. 2.—A. Case of long-standing Raynaud's disease showing bilateral superficial gangrene of finger tips.

B.



B. Complete healing of ulcerative areas shortly after bilateral dorsal sympathectomy.

TREATMENT

The majority of the patients in this series were not treated actively but were advised to stop smoking, to attempt to control their emotions if these played a role in precipitating the color changes, to live in a warm environment if possible, to try to avoid exposure to cold, and to dress warmly if this were not feasible. Sympathetic ganglionectomy was resorted to if the number and severity of the attacks were distressing or incapacitating or if nutritional disturbances existed. The operation was performed upon seven patients, fourteen extremities being sympathectomized. All four limbs were denervated in one patient; both upper limbs were denervated in three; both upper limbs and one lower limb in one; and one upper limb was denervated in two patients. In all patients except possibly one the immediate therapeutic effects were excellent. In the exception, all four extremities were sympathectomized in four stages. Although at each operation the patient felt sufficiently relieved to desire to have the next, at the completion of the procedure he was in doubt as to the total benefit. He no longer had any attacks of digital syncope and demonstrated a relatively stable circulation in his extremities, but he stated that he had some tingling in cold weather and annoying, and at times incapacitating, hyperhidrosis of the trunk in warm weather. The remaining patients upon whom this therapeutic procedure was done subsequently developed warm, dry, well-colored extremities, which tended to cool slowly upon exposure to cold. For the most part, attacks of syncope were absent. Those patients with loss of pulp in the tips of the fingers had a striking restoration to normal following operation. The patient with gangrene of several fingers showed prompt healing of the lesions (Fig. 2,B).

DISCUSSION

It has been the general impression that transient episodes of color changes in the digits in the male are usually secondary manifestations of occlusive arterial disease. This opinion, however, is not supported by the observations in the present series or in one previously reported.⁷ In no instance was there any indication that obliterative arterial disease existed or that it might subsequently appear. Such results would therefore be in accord with the view that in the differential diagnosis of peripheral vascular disorders in men manifesting color changes, the possibility of Raynaud's disease should not be disregarded.

The question whether the stress and strain of Army life may have contributed to the precipitation of this disorder in our group of patients cannot be fully answered by an analysis of the data, although it appears unlikely that this factor played an important role. In a considerable number of individuals the attacks began in civil life, and in only one instance did they arise under conditions of combat or just prior to such activity. Emotional stress and excitement initiated the color changes in only five patients, or 10 per cent, of the series, while emotional instability or other neuropsychiatric disorders were found in 28 per cent. These figures are not dissimilar to those of Hines and Christensen,⁷ who reported that in only nine of their 100 male civilian patients did an attack result from emotional excitation, although functional or neurotic disorders were present in twenty-nine.

Nevertheless, one cannot rule out the hypothesis that military life may have been a factor in some patients in aggravating the condition or in bringing into activity a latent disturbance, since these soldiers were exposed to cold weather to a greater extent than they might otherwise have been.

One of the criteria generally accepted as necessary in order to make a diagnosis of Raynaud's disease is the bilateral and symmetrical involvement of the extremities. In a significant number of our patients, however, there was unilaterality of involvement either in the upper or in the lower extremities. It is possible that the earlier the condition is seen, the more frequently will the attacks be noted in one limb alone.

In one-half of the patients in this series a classical triphasic color reaction was not noted, although in other respects these cases were typical examples of Raynaud's disease. Such an observation supports the concept already mentioned that in the presence of transient attacks of either digital syncope or cyanosis, brought on by exposure to cold or emotion, the possibility of a diagnosis of Raynaud's disease should be entertained, provided no etiology can be established and signs of obliterative vascular disease are absent. Furthermore, it does not appear necessary in Raynaud's disease for either the cyanosis or the pallor to be replaced by rubor as a preliminary step to the return of normal color.

With regard to the treatment of Raynaud's disease, it can be stated that the present series confirms what is generally known; namely, that if the difficulty is severe or is progressive in character, if nutritional disturbances exist, or if the process cannot be controlled by proper climate, sympathectomy offers the best means of therapy. The early results are generally excellent. However, nothing can be deduced from this study as to the duration of the good therapeutic effect. If the severity of symptoms does not make it imperative, sympathectomy of all four extremities is to be avoided, because of the discomfort which may result from the extreme hyperhidrosis of the trunk in warm weather.

SUMMARY AND CONCLUSIONS

The present study is based upon an analysis of fifty cases of Raynaud's disease in men. In only one-half of the patients was the typical triphasic color change of pallor, cyanosis, and rubor observed. In the remaining one-half, one or even two of these responses were absent, although in each instance the initial alteration was either digital pallor or cyanosis.

Nutritional disturbances, consisting of alterations in the nails, thickening of the skin, loss of subcutaneous tissue, and ulceration and gangrene, were present in 16 per cent of the cases.

In none of the patients were signs of organic vascular disease noted.

On the basis of the available data, the conclusion is reached that the possibility of a diagnosis of Raynaud's disease should be entertained as readily in the case of men showing characteristic color changes in the digits as in women, provided no signs of arterial obliterative disease are noted.

It is not necessary for symmetry of involvement or for a triphasic color change to be present in order to make the diagnosis.

Emotion evidently plays a much less important role in eliciting the episode of color change in men than it does in women. Furthermore, the stress and strain of Army life are apparently not potent factors in the production of the disease.

With regard to therapy, sympathetic ganglionectomy is of definite value in the treatment of nutritional disturbances and in the presence of severe and incapacitating attacks, or if steady progression of the malady is noted. Under other circumstances a trial of conservative treatment is indicated.

The authors wish to express their appreciation to Captain Herbert H. Lampert and to Major Robert H. Smith for their assistance in the collection and analysis of some of the data.

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TRAUMATIC RUPTURE OF THE AORTA

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TRAUMATIC rupture of the aorta caused by blunt force injuries is considered to be a rare occurrence. In 1919 Jaffé and Sternberg¹ reported ten examples of this lesion, five of which occurred in flying accidents. The occurrence of such ruptures is mentioned briefly in the textbooks of legal medicine.²⁻⁴ Single cases have been reported occasionally.⁵⁻¹⁷ Recently, McDonald and Campbell¹⁸ again drew attention to this rare injury when they described two cases of traumatic rupture of the normal aorta in young adults.

The reason that traumatic rupture of the aorta is not better known lies in the fact that the lesion is discovered only at necropsy. The rapid death, the state of coma and shock in which the injured person remains until death, and the concomitant severe injuries of different parts of the body, which are present in all cases, make a diagnosis during life very difficult.

Traumatic rupture of the aorta is, as a matter of fact, not as infrequent as is generally believed. From approximately 7,000 autopsies performed during the six years from 1936 to 1942 at the Chief Medical Examiner's Office of New York City in the borough of Manhattan, seventy-two cases of traumatic aortic rupture were collected. The findings in these seventy-two cases will be presented and compared with the findings in twenty-four cases of spontaneous rupture of the aorta (dissecting aneurysm) which were collected from the same source.

TRAUMATIC RUPTURE OF THE AORTA

Age and Sex.—Of the seventy-two cases of traumatic aortic rupture, fifty-seven occurred in men and fifteen in women. The age distribution had a wide range. The seventy-two cases included two children under 10 years of age, two adolescents under 20 years, eight adults between 20 and 30 years, eight between 30 and 40 years, twenty-two between 40 and 50 years, eleven between 50 and 60 years, ten between 60 and 70 years, seven between 70 and 80 years, and two over 80 years of age.

Forty-two of the series were less than 50 years of age and except for the results of trauma, showed no visible gross pathologic changes in the aorta. In the thirty subjects over 50 years of age, sclerotic changes of the aorta of varying degree were present.

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Cause of the Injury.—The manner in which the accidents occurred differed greatly. In fifty-one of the seventy-two cases the injury was the result of an automobile accident. More pedestrians were victims of this injury than drivers or passengers of cars. In ten of this series rupture of the aorta occurred after a fall or jump from a considerable height. Two men were run over by subway trains. Two were killed in elevator accidents when the cars fell suddenly to the ground. In three instances the thorax was crushed by a direct blunt force (crate or stone). One man died from a rupture of the abdominal aorta after he had been kicked in the abdomen. In three instances the circumstances under which the rupture occurred could not be ascertained; the bodies were found floating in water.

Site and Direction of the Rupture.—In sixty-one of the subjects, the aorta had ruptured in only one site (Group 1) and in eleven instances the vessel was torn in two or more sites (Group 2). In fourteen cases (eight of Group 1, six of Group 2) the rupture was situated in the ascending aorta above the aortic cusps in the area where spontaneous rupture of the aorta usually occurs. The most frequent site of traumatic rupture was at the isthmus of the aorta below the origin of the left subclavian artery at the insertion of Botalli's ligament. In forty of the cases (thirty-eight of Group 1, two of Group 2) the tear was found in this area. In fifteen cases (twelve of Group 1, three of Group 2) the descending thoracic aorta was torn between the isthmus and the diaphragmatic opening. In three cases the site of the rupture was in the abdominal aorta. The site of the second and third tear in eleven cases of Group 2 varied considerably.

In almost all instances the rupture occurred in a transverse direction through the wall of the vessel. Only a few T-shaped or longitudinal tears were encountered. In sixty-four subjects the rupture was complete and perforated all layers of the wall, including the adventitia. In eight instances the rupture was incomplete; the adventitia was still preserved and was dissected from the media by the hemorrhage resulting from the rupture.

Concomitant Injuries.—In all seventy-two victims of traumatic rupture of the aorta there were other injuries of the body. Fractures of the sternum alone were found in two patients, fractures of thoracic vertebrae in four, fractures of the ribs of one or both sides in twenty-six, fractures of ribs and sternum in eleven, fractures of ribs and vertebrae in nineteen, and fractures of ribs, sternum, and vertebrae in six patients. Only four patients had no fractures of the thoracic bones.

In addition to fractures of thoracic bones, fractures of the skull, the pelvis and the extremities were found frequently. The rupture of the thoracic aorta was associated in all instances with more or less extensive lacerations of internal organs including the heart, pericardium, lungs, liver, spleen, kidneys, mesentery, and bladder.

Cause of Death and Time of Survival.—A slight but nonfatal hemorrhage into the pericardial sac was observed in those patients in whom the rupture was just above the aortic cusps. Hemopericardium with real cardiac tamponade, a fre-

quent finding in fatal spontaneous rupture of the aorta, was observed in only one instance of traumatic rupture. Apparently a cardiac tamponade did not occur more frequently in the victims of traumatic rupture because of concomitant lacerations of heart and pericardial sac through which the blood escaped into the chest cavities or because of a rapid developing internal hemorrhage from a second tear in the aorta or from lacerations of other large blood vessels or organs (spleen, liver).



Fig. 1.—Traumatic rupture of the aorta at the isthmus in a Negro woman who was hit by an automobile and survived seven hours. (Courtesy Milton Helpert, M.D., New York, N. Y.)

The cause of death in most subjects was severe hemorrhage. In some instances the hemorrhage was the result of the aortic rupture alone; in other instances the aortic hemorrhage was associated with hemorrhages resulting from injury to other parts of the body including the heart, other blood vessels, lungs, spleen, liver, kidneys, and mesentery. In many instances fractures of the skull and (or) bones of the thorax, pelvis, and extremities were contributory factors. A ruptured thoracic aorta frequently led to a hemorrhage into the mediastinal tissue and (or) the left or both chest cavities. Hemorrhage into the retroperitoneal tissue or the abdominal cavity followed rupture of the abdominal aorta.

In fifty-nine patients death followed the injury within one hour. In all of these instances the rupture was complete and extended through all layers of the wall. Six patients lived from one to three hours, three lived from five to seven hours, and four lived from twelve to eighteen hours after the accident. In eight instances in which the victims lived for at least three hours after the injury, the rupture was incomplete in that the adventitia was intact (Fig. 1).

In contrast with the infrequent studies^{1-18,34} of traumatic rupture of the aorta, spontaneous rupture, particularly in its relationship to idiopathic cystic necrosis of the media, has received wide attention.¹⁹⁻³³ In the autopsy material which was the source of the seventy-two cases of traumatic aortic rupture, twenty-four examples of spontaneous aortic rupture were also found. In none of the twenty-four patients was there any evidence of external trauma. Spontaneous rupture of the aorta is not the subject of this paper; however, some of the important findings in the twenty-four patients who were found to have died of this lesion will be presented so that these findings can be compared with the findings in the seventy-two patients who died of traumatic rupture of the aorta.

Eighteen of the twenty-four patients were men and six were women. The age at which death occurred ranged from 17 to 63 years. One instance of spontaneous aortic rupture occurred in a 17-year-old boy and was associated with coarctation of the aorta and a bicuspid aortic valve.³¹ A bicuspid aortic valve was found in two other cases of spontaneous rupture. Eight patients who developed spontaneous rupture were in the age group between 30 and 40 years, six between 40 and 50 years, and eight between 50 and 60 years, and in one case the lesion developed in a patient who was 63 years of age.

In twenty-two instances the rupture was situated in the ascending aorta, a short distance above the aortic cusps, in one instance at the origin of the innominate artery, and in one instance at the origin of the left carotid artery. The direction of the tear was horizontal in twenty patients, L shaped in two patients, and vertical in two patients. In two patients a second tear which formed a reopening of the dissecting aneurysm into the aorta was located in the arch of the aorta.

The cause of death in all twenty-four subjects was hemopericardium which resulted from the rupture of the dissecting aneurysm into the pericardial sac. In fourteen instances death was sudden. In eight instances the victims of this lesion were found dead. As far as could be learned, they had all been in good health before death; it can be assumed, therefore, that in these eight patients death had been rapid. In two patients the time of survival was known, one man died three hours and another died twenty-two hours after the onset of symptoms.

DISCUSSION

Necropsy studies show that the findings in the two forms of aortic rupture differ considerably. Some of these differences will be discussed.

In all of the twenty-four examples of spontaneous rupture the tear started within the media. The dissecting aneurysm which resulted ruptured into the pericardium and produced a fatal tamponade of the heart (Figs. 2 and 3).

In the seventy-two cases of traumatic rupture it was difficult to determine in which layer of the wall the rupture began, since in most instances the tear was complete and involved all layers of the wall. In a few patients who survived the accident from three to eight hours the adventitia was intact though dissected from the media by the hemorrhage which resulted from the tear. True dis-

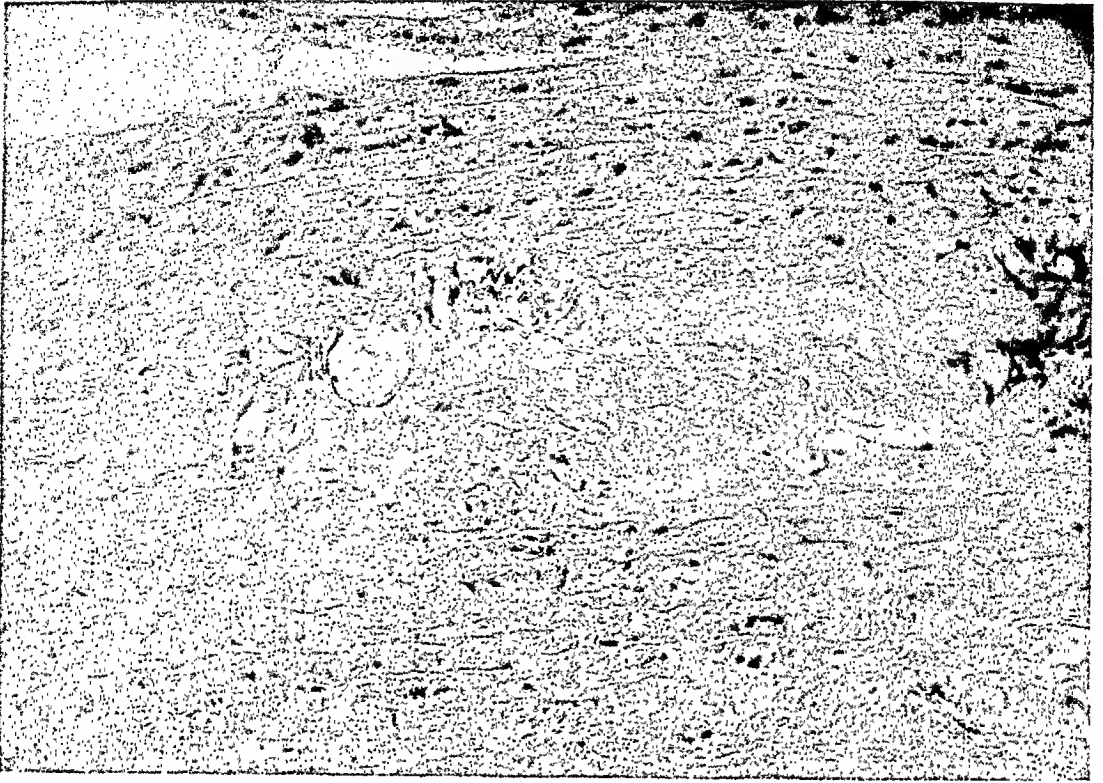


Fig. 2.—Spontaneous aortic rupture in a 50-year-old woman who was found dead. Medionecrosis cystica with mucoid degeneration. Hematoxylin and eosin stain; $\times 223$.

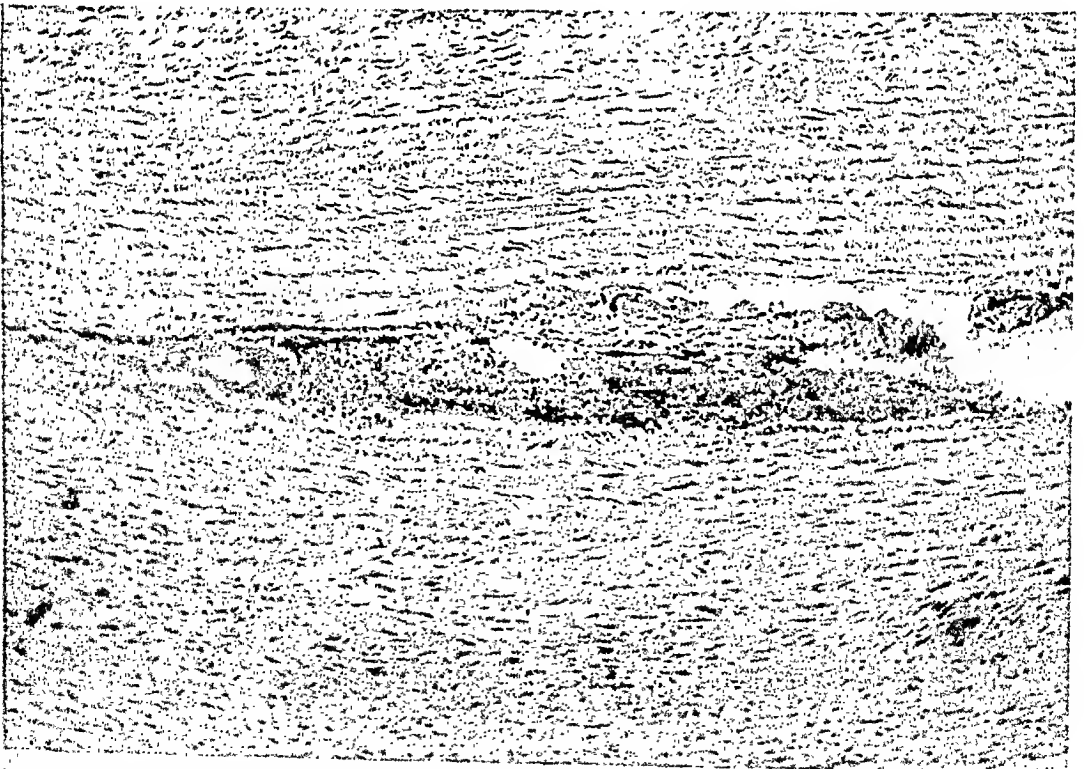


Fig. 3.—Spontaneous aortic rupture in a 50-year-old man who was found dead. Tear within the media with hemorrhage and cellular reaction. Hematoxylin and eosin stain; $\times 110$.

section within the media (as seen in spontaneous rupture) was not found in this series of patients; apparently it is rare in traumatic rupture. It seems probable that in a number of instances of traumatic rupture the tear begins in the intima. This is suggested by the fact that in several cases superficial intimal tears were present in some areas in addition to complete tears of the whole wall. In all but two of the patients with spontaneous rupture the site of rupture was a short distance above the aortic valves. The site of traumatic rupture was not nearly so consistent: the tear occurred in various portions of the aorta but most often at the isthmus.

It is generally assumed that one factor, medial cystic necrosis, mainly determines the site of spontaneous rupture. On the other hand, many factors determine the location of aortic rupture due to trauma. A possible reason why the majority of traumatic ruptures develop at the isthmus of the aorta is the fact that the aorta is narrowed and relatively fixed at this site by the attachment of Botalli's ligament. This might render this portion of the vessel more subject to overextension or twisting or sudden increase of intra-arterial pressure. In all but four patients fractured vertebrae and (or) ribs and sternum were present. In many instances the aortic rupture was the result of laceration by sharp bone fragments. In four patients no fractured thoracic bones were present. Lacerations by sharp fragments of bones obviously did not determine the site of the rupture in all instances. Overextension or twisting of the vessel are among other possible factors. In the three patients in whom the site of rupture was in the abdominal aorta the rupture appeared to have been caused by the effect of the blunt force compressing the aorta against the vertebral column. This opinion is particularly supported by the fact that no fractures were present in one case. The same mechanism may explain the occurrence of some traumatic ruptures of the thoracic aorta. Sudden increase in intra-arterial pressure, causing a bursting rupture from within, appeared to play an important role in producing rupture of the aorta. This is the most likely explanation of the rupture in the three young patients (with elastic thoraces) in whom there were no nearby bone fractures and little evidence of external injury.

Although arteriosclerosis of the aorta was present in the older victims of traumatic rupture, the wide age distribution of the series as a whole suggests that this was not important in determining the development or the site of the aortic rupture. In three of the victims with spontaneous rupture a congenital defect was present and conceivably may have played a role in the development of the lesion. No congenital defects were present in any of the victims with traumatic rupture.

The immediate cause of death in all patients with spontaneous rupture of the aorta was a rupture of the resulting dissecting aneurysm into the pericardium and fatal cardiac tamponade. Although one patient in the series of traumatic aortic ruptures developed this lesion, the remainder of the patients died of internal hemorrhage into the chest or abdominal cavity or into retroperitoneal or mediastinal tissues.

In both forms of aortic rupture more men than women were victims of the accident. The medicolegal source of the material may have determined this fact.

The source of the material may also be responsible for the fact that healed spontaneous rupture, reports of which are not infrequent,^{6,23,31,33} was not found more often in this series of patients.

SUMMARY

Seventy-two cases of traumatic rupture of the aorta and twenty-four cases of spontaneous rupture have been reviewed and compared. The main differences regarding occurrence, origin, and pathologic picture of both lesions have been discussed.

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Clinical Reports

ANEURYSMAL DILATATION OF THE AORTA ASSOCIATED WITH CYSTIC MEDIAL NECROSIS

CASE REPORT

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SINCE Erdheim's^{1,2} description of a new pathologic entity, idiopathic cystic medial necrosis of the aorta, most of the articles published on this subject have dealt with its relation to dissecting aortic aneurysms. A detailed review of this aspect of the disease may be found in the excellent articles of Sailer,³ Rottino,⁴ and Moritz.⁵

Similar pathologic lesions have been found only rarely in unruptured aortas. Rottino⁶ reported seven such cases in a routine study of 210 specimens. Moritz⁵ found defects of the tunica media in six of a total of seventy aortas that he studied. In these cases, as in those where dissecting aneurysms were present, the lesions were most numerous in the ascending aorta and the first part of the aortic arch. They were often, but not always, found in elderly patients with a history of antecedent hypertension.

In addition to these reports a small number of cases have been described in which cystic medial necrosis was found to be the only pathologic change in the walls of large aneurysms of the ascending aorta. The majority of these cases had associated aortic regurgitation that was clinically demonstrable. The incompetency of the aortic valve was due to the dilatation of the aortic valve ring and not to lesions of the valve cusps.

The case reported by Rottino⁷ was that of a 70-year-old woman. This patient did not have aortic regurgitation. The aneurysm was 12.5 cm. in circumference and involved most of the ascending aorta. The aortic arch and aortic valve ring were involved to a much less degree. The intima was wrinkled and appeared grossly to resemble syphilitic aortitis. There was, however, no evidence of syphilitic changes when microscopic examination was made. Instead, the typical cystic areas and elastic tissue and muscle disruption of medial necrosis were found.

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Baer and co-workers⁸ described two patients with arachnodactyly, both of whom died from cardiac decompensation due to aortic regurgitation secondary to large saccular aneurysms of the ascending aorta. One patient who died at the age of 14 years also had an associated patent foramen ovale and had been observed from birth. Cardiac murmurs had always been present. The other patient died at the age of 26 years. In neither case had the dilatation of the aorta been evident on roentgenologic examination. The circumferences of the aneurysms were 14 cm. and 19 cm., respectively. Pathologically the only lesions found to explain the presence of the aneurysms were those of cystic medial necrosis. It was the opinion of Baer and associates that this might more likely represent a congenital defect of the media rather than a degenerative process.

Another case in which arachnodactyly was present was reported by Etter and Glover.⁹ Unfortunately no microscopic studies were reported so that one cannot be certain that cystic medial necrosis was present. However, the association of arachnodactyly with dilatation of the aorta, aortic regurgitation, and death, finally, due to the rupture of a dissecting aneurysm suggests that the case may belong in this group. The patient was 21 years of age at the time of death. The aortic regurgitation could have been due either to dilatation of the ascending aorta, as in the other cases described, or to the presence of a chronic dissecting aneurysm, as in the patients described by Gouley and Anderson.¹⁰

Our patient failed to show arachnodactyly but the clinical and pathologic findings were strikingly similar to those described by Baer and collaborators.⁸

CASE REPORT

E. Z., a 29-year-old white man, who worked as an attendant in a service station, entered the Los Angeles County General Hospital on July 18, 1945. The chief complaints were shortness of breath for four weeks and swelling of the legs for two weeks. He stated that he first learned that he had heart disease in 1942, when he was rejected by the Army for that reason. Since that time he had noticed palpitation of the heart and attacks of dyspnea that occurred about once a month. These were not accompanied by edema or fever and were not incapacitating. During the four weeks before admission he had experienced severe weakness and dyspnea on exertion which had forced him to cease working. Gradually the dyspnea increased until it was present at rest; for the last two weeks he had noticed edema of the feet and legs which slowly extended to the thighs and scrotum. He had a cough which had been productive of small amounts of blood-tinged sputum. He consulted his family doctor who advised admission to the hospital. He stated that he had had asthma most of his life. The attacks had been more severe and frequent since the age of 13 years and seemed to be precipitated by exposure to dust and grain. There was no history of familial disease except that his brother also had asthma. His mother had died during the influenza epidemic of 1918. The patient denied any history of rheumatic fever, rheumatic symptoms, syphilis, or antisyphilitic therapy. His only previous illnesses were rubeola as a child and pneumonia in 1937. He had had a tonsillectomy at the age of 10 years. He considered that he had had a healthy childhood and had always been able to exercise as long and as hard as other children of his age.

Examination revealed a fairly well-developed and well-nourished young man who was orthopneic and dyspneic. The vital signs were pulse, 120; temperature, 98.6; respirations, 24 per minute; and blood pressure, 115/50 in the right arm. The eyes showed slight but definite arcus senilis bilaterally. The fundi were normal. There were numerous expiratory asthmatic wheezes throughout both lung fields and inspiratory subcrepitant râles and rhonchi at both lung bases. The heart was markedly enlarged. The point of maximum impulse was visible and palpable in

the sixth intercostal space at the anterior axillary line. There was a palpable systolic thrill over the sternum. The rhythm was that of sinus tachycardia. The first sound was reduplicated over the whole precordium. At times a gallop rhythm was heard. There was a short rough systolic murmur at the aortic area with a loud blowing diastolic murmur that radiated down the left sternal border. There was a loud rough systolic murmur at the apex. The pulse was of the water-hammer type and Duroziez's murmur was prominent over the peripheral vessels. The brachial arteries were easily compressible. The liver edge was palpable 10 cm. below the right costal margin. The abdomen was slightly distended and signs of free peritoneal fluid were present. No other abdominal organs or masses were palpable. Scrotal edema and pitting edema of the feet, legs, and thighs were present. The reflexes were physiologic.

Hemoglobin was 14.0 Gm. per 100 c.c.; erythrocytes, 4,300,000 per cubic millimeter; and leucocytes, 8,550 per cubic millimeter. The differential count was normal. Sedimentation rate (Wintrobe) was 1 mm. per hour. Examination of the urine was normal. Blood chemistry was as follows: nonprotein nitrogen, 40 mg. per 100 c.c.; blood chlorides (as NaCl), 480 mg. per 100 c.c.; albumin: globulin ratio, 4.7/2.2 Gm. per 100 cubic centimeters. Blood Kolmer and Kahn reactions were negative. Blood culture showed no growth. An electrocardiogram is shown in Fig. 1.

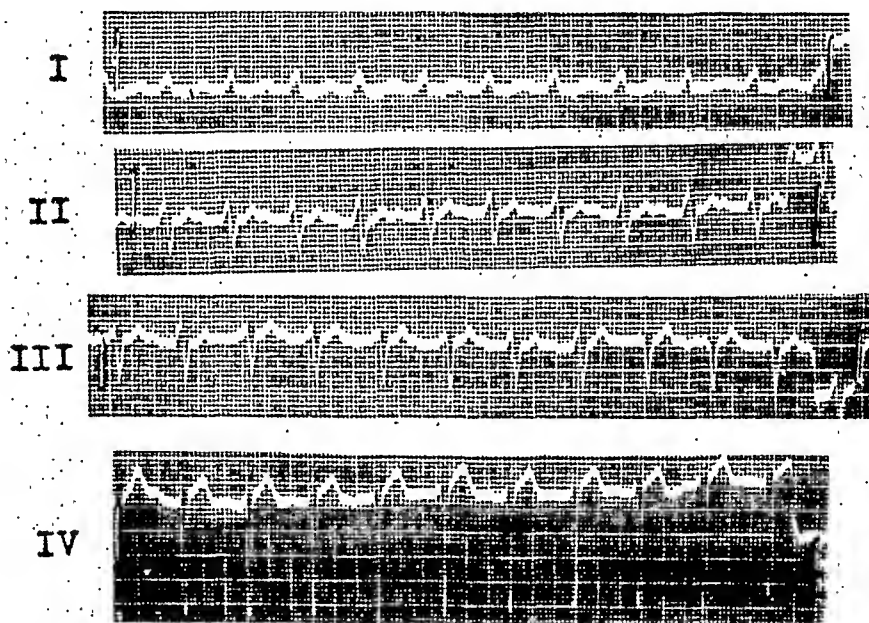


Fig. 1.—Electrocardiogram. Sinus tachycardia, rate, 110 per minute. Prolonged auriculoventricular conduction. P-R interval, 0.24 second. QRS interval was 0.14 second and the configuration was that of typical left bundle branch block. The maximum height of the R wave in the chest lead (IV F) was 1 millimeter. Two other electrocardiograms taken showed no changes.

The patient was digitalized and was given aminophylline and mercurial diuretics intravenously. Anionium chloride and ephedrine were taken orally. He experienced an adequate diuresis and became less dyspneic but about a week after admission suffered severe attacks of asthma that were relieved by epinephrine, aminophylline, or ephedrine. He died suddenly on July 31, 1945, thirteen days after admission to the hospital.

The etiology of the cardiac disease was variously considered by different members of the clinical staff as rheumatic heart disease, congenital abnormality of the aortic valve, syphilitic aortitis, or calcific aortic stenosis with bacterial endocarditis.

Autopsy.—*

*Performed by I. I. L.

Anatomical Summary: The body was that of a well-developed, well-nourished white man, approximately 29 years of age, weighing 68 kilograms and measuring 175 cm. in length. There were semilunar areas of arcus senilis in both eyes.

Upon opening the thorax the heart was found to occupy a tremendous volume of thoracic space. The apex of the heart was found at the seventh intercostal space in the midaxillary line. The aortic arch as it leaves the heart was noted to be greatly widened. The heart weighed 900 grams. The pericardium was smooth and glistening. There was myocardial hypertrophy of the entire heart. The endocardium was smooth and glistening. On the aortic valve were found two verrucous-like vegetations approximately 1 mm. in diameter. No growth was evident on culture. However, on subculture an anaerobic strain of *Staphylococcus albus* was obtained. The valves measured as follows: mitral, 12.5 cm.; aortic, 12 cm.; pulmonic, 9 cm.; and tricuspid, 15 centimeters. The left ventricular wall was 19 mm. and the right, 6 mm. in thickness. The chambers of the heart were extremely dilated. The ascending portion of the aorta was tremendously enlarged into a bulging pouch which was 22 cm. in circumference. This continued for a distance of approximately 5.7 cm. superiorly, at which point the aorta abruptly narrowed down to a circumference of 5.8 centimeters. The intima of the dilated part of the aorta was wrinkled. The coronary arteries appeared to be grossly normal. The ostia, however, were somewhat occluded by a slight degree of distortion at their origin. The two arteries took origin in the normal place in regard to the aortic cusps but appeared to arise higher than usual. They were found 1.5 cm. above the edge of the aortic valve. The ostia were, however, patent. Fig. 2 shows



Fig. 2.—Detailed photograph of aorta. The aortic valve is tricuspid.

these changes. The interauricular septum was patent in the superior portion of the foramen ovale. This patency measured approximately 1.5 cm. in diameter. The chordae tendineae of the heart muscle were of normal size. The papillary muscles similarly appeared grossly normal. Several sections were taken from various places in the heart for microscopic study.

The pleurae were smooth and glistening. The right lung weighed 650 grams and the left, 640 grams. There was moderate chronic passive congestion. The pulmonary arteries were normal. There was approximately 150 c.c. of clear yellowish fluid in the right pleural cavity and 100 c.c. in the left pleural cavity. It was a transudate.

There was chronic passive congestion of all the viscera.

Microscopic Findings: The kidney, spleen, liver, and pancreas showed chronic passive congestion.

Sections from the lungs showed passive hyperemia. The lung capillaries were distended with red blood cells. The bronchial walls were thickened. There was no mucinous degeneration of the epithelium noted. The subepithelial tissue exhibited an increase in fibrous connective tissue. These same areas were infiltrated with round cells. There was evidence of extensive vascularity in the subepithelial connective tissue, as though chronic inflammatory change was present. The smooth muscle tissue was hypertrophied. Some of the bronchi contained an exudate consisting of fibrin, round cells, red blood cells, and an occasional eosinophil.

Papillary muscle of the heart showed considerable scarring. Some areas were fibrosed and there was revascularization. In the myocardium hypertrophy and small areas of interstitial fibrosis were seen.

DISCUSSION OF PATHOLOGY

Serial sections were made of the aorta. The pulmonary artery exhibited no evidence of pathologic change. In and about the area of the aneurysm the most marked medial change was noted. The transverse and descending aorta were found to be grossly unchanged by any cystic medial necrosis, although even in these areas slight cystic medial degeneration was seen. The most marked changes were seen in the sections taken from the center of the aneurysmal dilatation just above its origin near the aortic valve. The hematoxylin and eosin stain



Fig. 3.—Large cystic focus in media of ascending aorta. Hematoxylin and eosin; magnification $\times 125$.

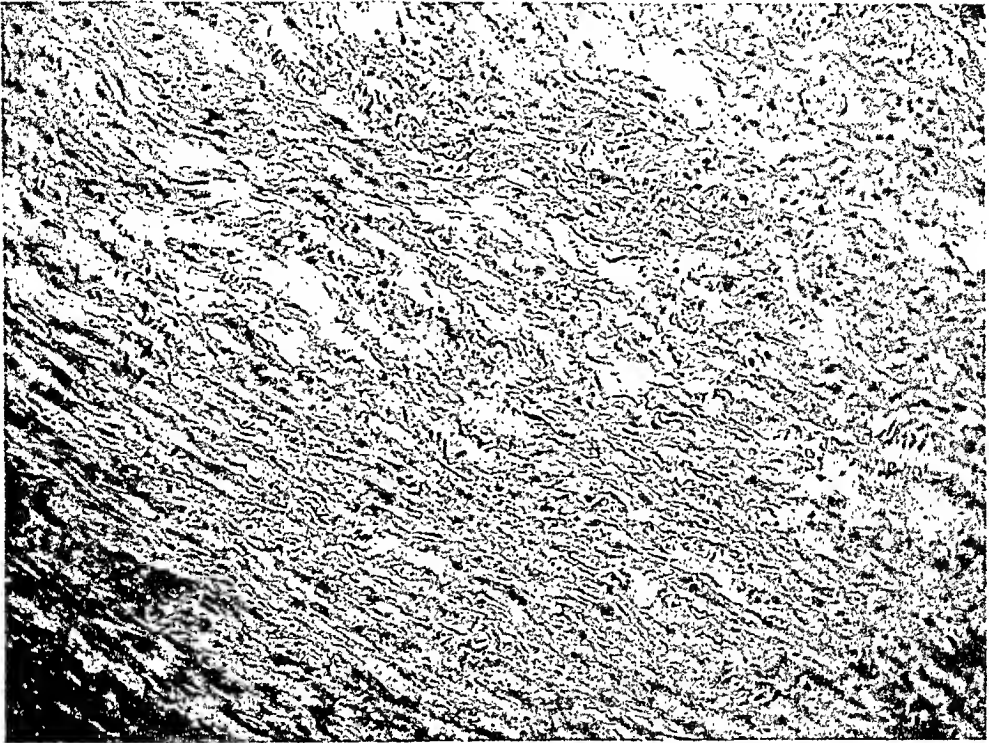


Fig. 4.—Cystic areas in media of ascending aorta. Polychrome methylene blue; magnification $\times 180$.

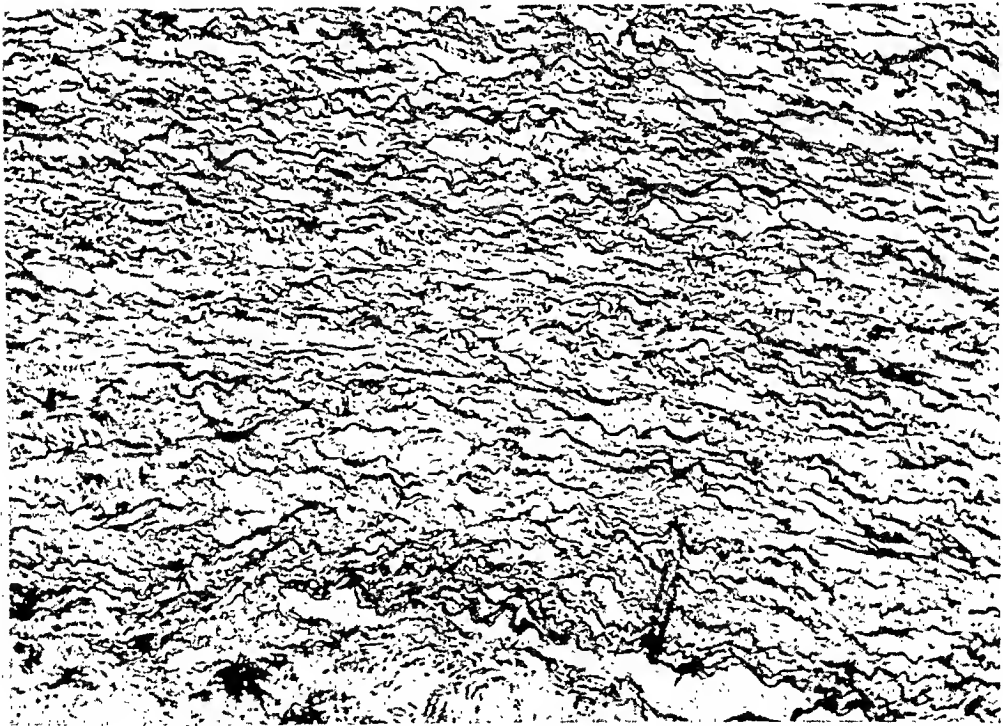


Fig. 5.—Fragmentation and displacement of the elastic fibers of the media. Orcein; magnification $\times 180$.

showed several large cystic areas in the media, which are the characteristic lesions of the cystic medial necrosis originally described by Erdheim (Fig. 3). The polychrome methylene blue stain exhibited a marked color contrast in that the cystic areas stained a light pink color (Fig. 4). The orcein stain showed a marked displacement of the otherwise orderly elastic fibers (Fig. 5). Fat stain demonstrated small areas of free fat in and about the cystic area as well as in macrophages in the cystic area.

SUMMARY AND CONCLUSIONS

A case of aneurysmal dilatation of the ascending aorta due to cystic medial necrosis of the aorta is presented. The gross appearance of these lesions is such that it may be confused with syphilitic aortitis if microscopic studies are not made. It is suggested that this diagnosis be considered in youthful patients with dilatation of the ascending aorta, aortic regurgitation, and associated congenital defects in the absence of syphilis, hypertension, and a rheumatic history.

Because of the not uncommon association of cystic medial necrosis of the aorta with other congenital defects, such as arachnodactyly and patent foramen ovale, and because of the similarity of the pathologic changes to those seen in some fetal blood vessels, it is our opinion that this lesion can be most likely explained on the basis of a congenital defect of the media of the aorta.

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WOLFF-PARKINSON-WHITE SYNDROME PRESENTING CERTAIN UNUSUAL FEATURES

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THIS interesting disturbance of the cardiac conduction mechanism has received considerable comment in recent years. Some six patients presenting this abnormality have been seen in a regional station hospital in the past thirty months. The case report submitted is of a soldier in whom symptoms were more pronounced than in most of the cases described in the literature.

A white soldier, 22 years of age, was first seen at this hospital in September, 1943, when he was referred from the dispensary of his organization because of complaints of periodic attacks of rapid heart rate, dizziness, nausea, and precordial pain. The pain was sharp in character and was associated with the attacks of rapid heart action. He stated that he first noticed symptoms in 1940. An attack of rapid heart rate with dizziness had developed as he sawed wood on a farm in Midwestern United States. This persisted all day. This first attack had been followed by several similar attacks of shorter duration. He was unable to incriminate any particular activity as a cause but felt that many attacks were precipitated by sudden effort. Each attack began abruptly and ended similarly. Often he was conscious of a thumping sensation in the lower left chest as the attack ended. Lying down usually caused an attack to disappear. Once or twice during the attacks the legs had become swollen, but he had never developed a cough or produced any sputum during the attacks.

General physical examination on the occasion of this admission showed a robust individual weighing 175 pounds. No abnormalities of the skin were noted. There was no obvious dyspnea nor cyanosis. The lymph nodes were not enlarged. The lungs appeared normal. No definite enlargement of the heart was found on clinical examination nor were any significant irregularities of its action nor any important murmurs detected.

Routine urinalysis and blood count showed no abnormal findings. The blood Kahn reaction was negative.

A roentgenogram of the chest was considered normal. Chest fluoroscopy showed no enlargement of any of the chambers of the heart.

An electrocardiogram (Fig. 1) was considered to be normal.

After a few days of observation, the patient was returned to duty. During the hospital stay he exhibited no evidence of being dyspneic and no cardiac irregularity was detected.

Early in January, 1944, he was readmitted because of a papulomacular rash which had been first noted some two days after possible exposure to venereal disease. The eruption spread to involve the skin of the chest and abdomen. It was intensely itchy and was associated with a slight photophobia. The soldier was placed in an isolation ward and on the day following admission the eruption was replaced by a discrete pustular type of lesion developing in crops and suggesting chicken pox. Three days after admission a urethral discharge was noted which on culture was found to contain gonococci though the smears of the purulent discharge failed to show any such organisms. Treatment with sulfadiazine was instituted and the urethritis rapidly

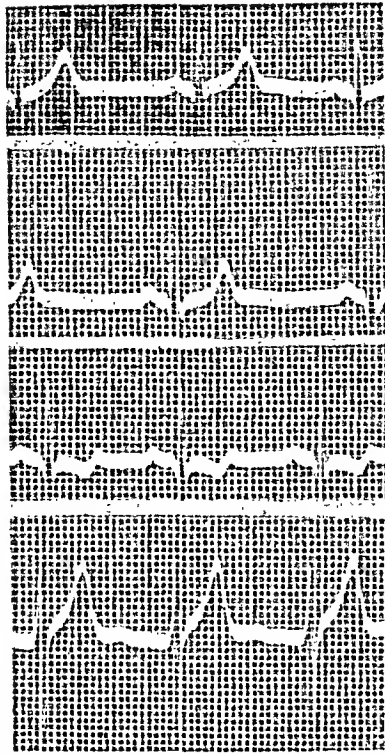


Fig. 1.—Electrocardiogram taken on Sept. 25, 1943.

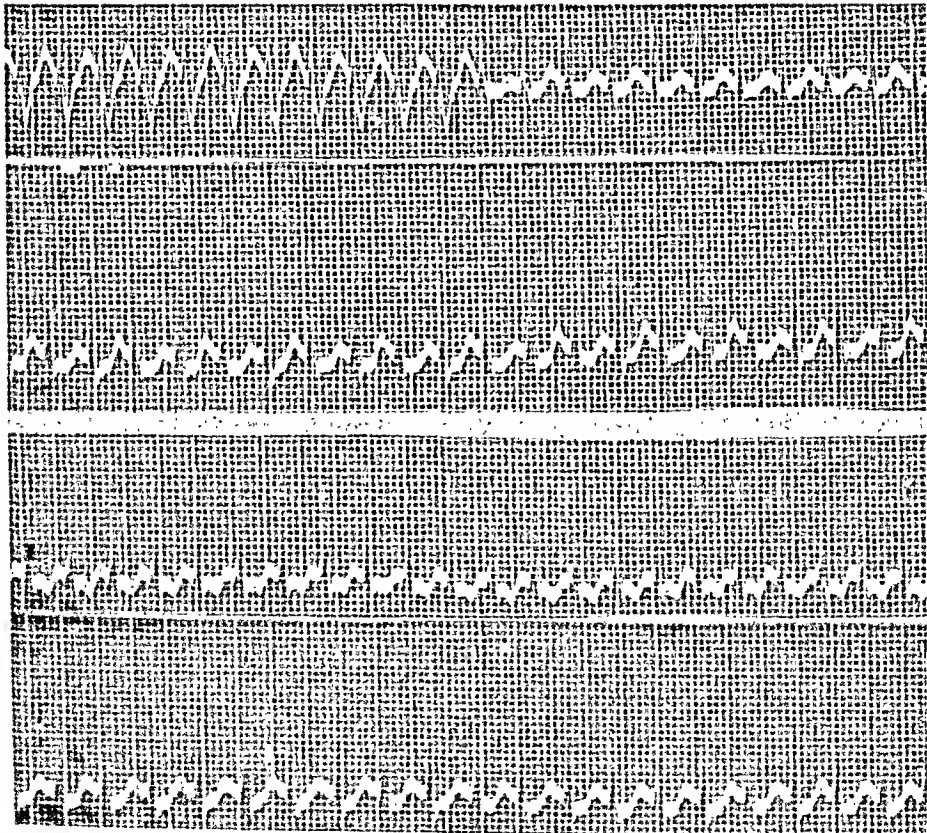


Fig. 2.—Electrocardiogram taken during an attack of paroxysmal tachycardia. Note the abrupt transition from one type of paroxysm to another.

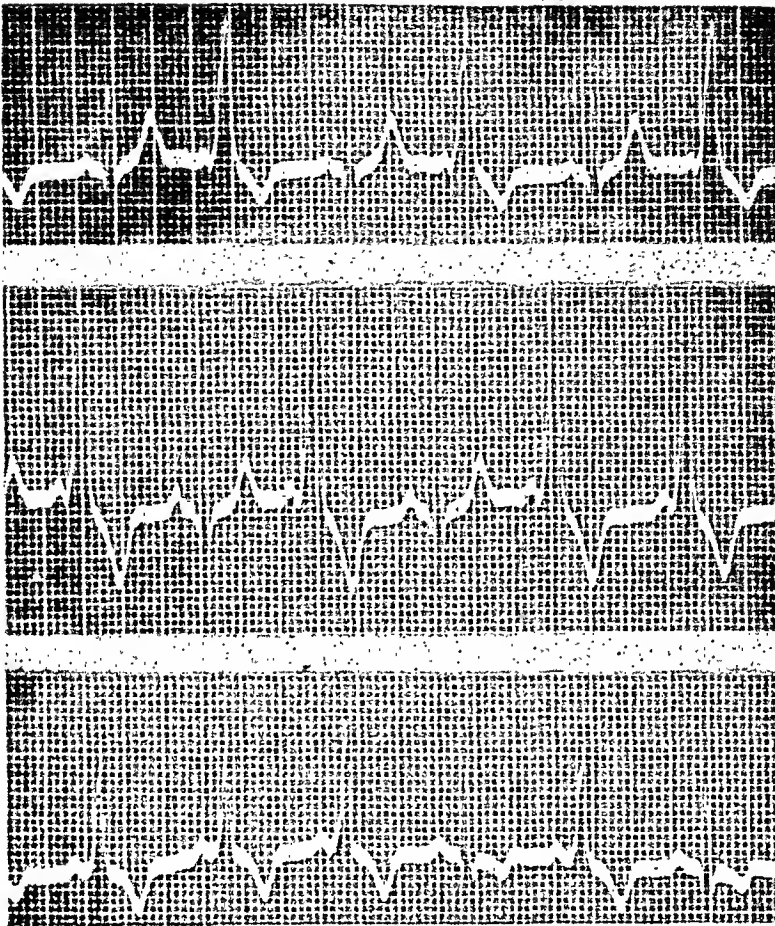


Fig. 3.—A normal complex alternating with abnormal complexes showing short P-R intervals with evident widening of the QRS complexes and inverted T waves. Only Leads I, II, and III are shown.

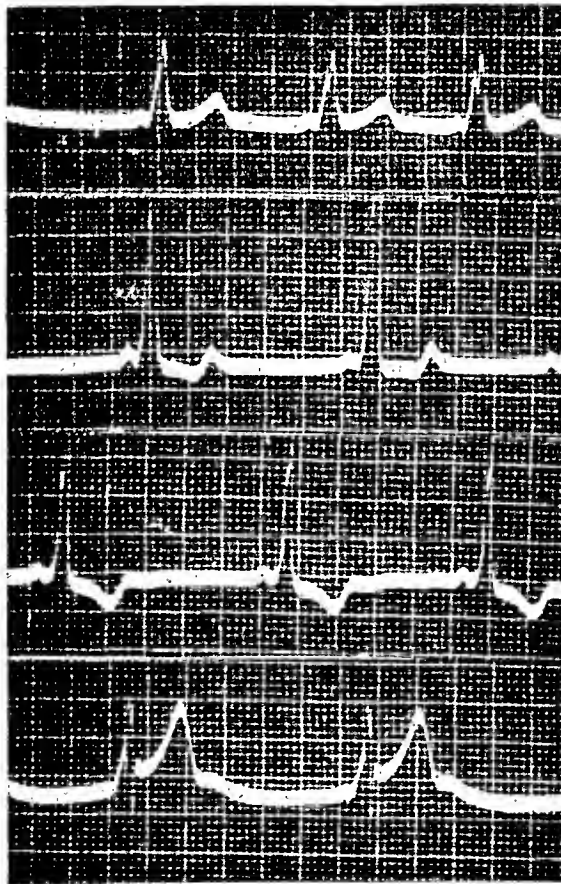


Fig. 4.—An electrocardiogram taken in December, 1942. The P-R interval is recorded as 0.08 second. The QRS duration is 0.14 second.

cleared. The skin rash disappeared within four days of admission. On Jan. 17, 1944, about 10:00 A.M., the patient suddenly developed an attack of weakness. It was noted that he was moderately dyspneic but not cyanotic. He did not cough. The radial pulse beat was rapid; a definite count could not be made. An electrocardiogram was taken immediately (Fig. 2). It showed a tachycardia which was apparently of two types. The first eleven complexes shown in Lead I conform to those seen in a ventricular tachycardia. This type of rhythm changed abruptly to a supraventricular rhythm of approximately the same rate. The latter suggested an A-V nodal type of paroxysmal tachycardia. From past experience, the soldier knew that by his lying supine in bed without moving the rapid rate would soon subside. Attempts to abort the attack by carotid pressure were without result. Within five minutes the rate suddenly slowed. This slowing was initiated by his noting a thumping sensation in the lower left chest. This occurred as the lead wires were being changed and is not recorded on the electrocardiogram. However, when the electrocardiogram was examined it was found that an apparently normal complex alternated with a complex presenting a short P-R interval (0.08 second), a widened QRS complex (0.12 second), and an inverted T wave in Leads I, II, and III (Fig. 3).

Further inquiry revealed that the patient had been subject to attacks of hay fever earlier in his life and had been given various types of medication for this. His first attack of tachycardia developed during an attack of sneezing. He had been told by a physician who had examined him sometime before he entered the Army that his electrocardiogram was abnormal. Because of this, shortly after his entry into the Military Service, he had been examined at an Army hospital. An electrocardiogram taken there in December, 1942, was requested and on examination was found to show a short P-R interval in all complexes, a widened QRS complex, with, however, an upright T wave in Lead I (Fig. 4).

Quinidine, 0.6 Gm. daily, was begun but seemed to have little effect. The electrocardiogram returned to normal; it was never apparent whether this occurred spontaneously or was a result of therapy. While at rest the soldier was comfortable, exhibiting no symptoms of illness. A cardiac murmur was not heard and at no time, clinically or by roentgenogram, could any cardiac enlargement be found.

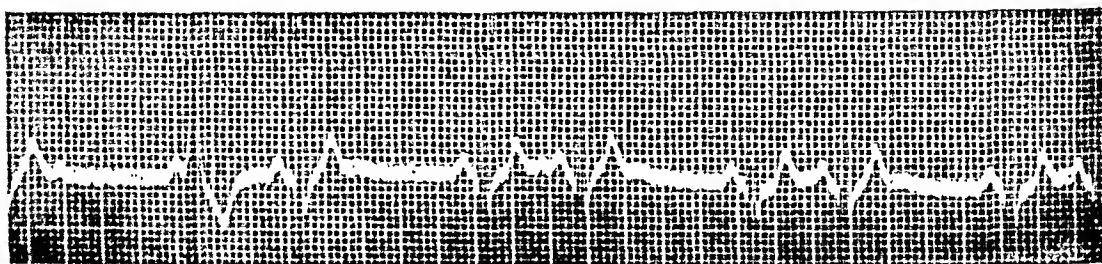


Fig. 5.—Electrocardiogram showing a coupling of normal complexes with an occasional abnormal complex.

The patient soon discovered that activity such as running a city block on smooth terrain resulted in the development of tachycardia. Usually this was supraventricular in type, but occasionally one or two widened complexes suggesting a ventricular tachycardia interjected themselves in the record. Occasionally, as is shown in Fig. 5, a peculiar coupling of normal complexes was demonstrated. This suggested a "sinus arrest." Resumption of a regular slow pulse rate always resulted from his lying supine for a few minutes and no other attempts at aborting an attack were considered. Epinephrine, 0.5 c.c. hypodermically, produced the same results as physical activity.

It became apparent that the soldier's disability was incapacitating and he was discharged from the Army.

The case which has been described presents the classical features of what has come to be known as the Wolff-Parkinson-White syndrome.¹ Commonly it is a source of little inconvenience to a patient unless the attacks of tachycardia are difficult to stop or last for long intervals. The widened QRS complexes of this syndrome must be sharply separated from the widened complexes of intraventricular or bundle branch block with their more ominous significance. Most cases described have shown a supraventricular type of tachycardia. In 1941, Levine and Beeson² described three cases and referred to the infrequency of occurrence of ventricular tachycardia in this condition.

SUMMARY

A case of Wolff-Parkinson-White syndrome occurring in a young man is presented. It is felt the electrocardiographic findings which are described may serve to assist in the elucidation of some of the unsettled problems concerning the exact mechanism of this abnormality.

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PULMONARY EDEMA IN THE PREGNANT PATIENT WITH MITRAL STENOSIS

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INJUDICIOUS administration of intravenous fluids is a not uncommon cause of acute pulmonary edema. Patients with mitral stenosis are particularly susceptible to this hazard, especially during pregnancy. Two cases, recently under our care, clearly exemplify this danger.

CASE REPORTS

CASE 1.—Mrs. E. M. T. H., a 29-year-old primigravida, was first seen in the prenatal clinic June 13, 1944. She gave a definite history of chorea and heart disease in childhood and stated that her father, a physician, had urged her to be careful of her heart. Routine examination however, was normal and the patient felt quite well throughout the pregnancy, having gained thirty-five pounds in weight. At no time did she experience any dyspnea, orthopnea, edema, or other evidence of limited cardiac reserve. Labor began Jan. 4, 1945, and was prolonged by a persistent occiput-posterior position and uterine inertia. After fifty-two hours of fairly hard labor, she was delivered by mid-forceps, under spinal anesthesia, with the use of Kjelland's forceps for rotation. During this prolonged labor it was thought advisable to give the patient supplementary fluids. Accordingly, she received five separate intravenous infusions, each of 1,000 c.c. of 5 per cent glucose in saline, at twelve-hour intervals. The last of these infusions was given one hour before delivery. In the delivery room she received 1 unit (250 c.c.) of plasma before delivery and 500 c.c. of citrated blood afterward. She appeared well for the next ten hours, after which she complained of gradually increasing dyspnea.

Examination revealed slight cyanosis with difficult breathing. Râles were present throughout both lungs. The temperature was 99.2°F.; pulse, 100; and respirations, 28 per minute. The white cell count was 12,700. A clinical diagnosis of pneumonia was made and she was treated with penicillin, sulfadiazine, and oxygen for forty-eight hours without definite improvement. X-ray examination of the chest showed mottled infiltration of both lung fields, some fluid in the left costophrenic sinus, and enlargement of the heart. The radiologic interpretation was congestive heart failure. When seen by a medical consultant, a to-and-fro mitral murmur was heard at the apex. Moist râles were present throughout both lung fields. There was no enlargement of the liver, no noticeable distension of the neck or peripheral veins, and no demonstrable peripheral edema. Digitalis was prescribed, the fluid intake was restricted to 1,500 c.c. daily, and oxygen therapy was continued. The penicillin and sulfadiazine were discontinued.

From this time, improvement was rapid and at the end of sixty hours all clinical evidences of pulmonary edema had disappeared. The mitral systolic and diastolic murmurs gradually diminished in intensity so that two weeks later a rumbling mid-diastolic murmur could be elicited only by careful auscultation. X-ray examination showed normal lung fields and an essentially normal cardiac silhouette. Six weeks after delivery no murmurs at all could be elicited. She has remained well since.

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Summary.—A young woman with "silent" mitral stenosis of long standing had never experienced any cardiac symptoms. Pulmonary edema developed ten hours after a long, hard labor, during which she received intravenous fluids.

CASE 2.—Mrs. J. H. H., a 27-year-old secundigravida, was first seen in the prenatal clinic in April, 1945, during the third month of pregnancy. She gave a history of chorea at 8 years of age with annual recurrences until she was 18 years old. She had never known of heart disease and six years previously had gone through a normal pregnancy without difficulty. Examination in the cardiac clinic disclosed a localized rumbling diastolic murmur at the apex. The clinical diagnosis of mitral stenosis was confirmed by x-ray examination which showed straightening of the left upper heart border in the postero-anterior view and pressure by the left auricle on the barium-filled esophagus in the left lateral view.

Her course was uneventful until July 4, 1945, when she was admitted to the hospital because of acute pyelonephritis. The night of admission she received 1,000 c.c. of 5 per cent glucose in saline without untoward effect. The next morning another infusion of 5 per cent glucose in saline was started. After fifteen minutes of moderately rapid flow, she suddenly developed severe dyspnea. On examination she was dyspneic and cyanotic and coughed frequently. There were numerous loud râles in both lungs. X-ray examination showed disseminated densities throughout both lung fields which suggested congestive failure. This emergency was treated promptly by the use of alternating tourniquets on all four extremities and by the administration of morphine, atropine, oxygen, and digitalis. Within three hours she was fairly comfortable so that the tourniquets were removed. Ten hours later she experienced a mild relapse. Again, rapid relief was obtained by the use of the tourniquets. There were no further recurrences of pulmonary edema and the next day she felt perfectly comfortable. At the end of two weeks she was allowed out of bed for short periods and three weeks later was delivered by classical cesarean section under local anesthesia without untoward effects.

Summary.—A young woman in the eighth month of pregnancy, with classical manifestations of mitral stenosis, but who had never been in failure nor had experienced any limitation of activities, suddenly developed acute pulmonary edema in the course of an intravenous infusion of 5 per cent glucose in saline. She responded quickly to therapy and was delivered five weeks later by a classical cesarean section.

DISCUSSION

The dynamic equilibrium in the pulmonary circulation of pregnant patients with mitral stenosis is easily upset. Both the physiologic hydremia of pregnancy and the mechanical obstruction by the narrowed mitral diaphragm tend to cause pulmonary engorgement. Intravenous fluids may thus lead to acute pulmonary edema more readily than in normal individuals.

It is suggested that special precautions be taken in such patients as to the route of administration, rate of flow, and total quantity of parenteral fluids. The two cases reported here emphasize the fact that good exercise tolerance and inconspicuous physical findings may give a false sense of security.

SUMMARY

The occurrence of pulmonary edema, in association with pregnancy, in two young women with mitral stenosis is reported. Neither patient had had any previous cardiovascular symptoms. In both patients the pulmonary edema followed the parenteral administration of large amounts of fluid.

CHRONIC FIBROPLASTIC MYOCARDITIS

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CLINICIANS and pathologists frequently encounter cases of cardiac hypertrophy, with or without fibrosis, in young people. These cases are often not associated with the usual causes of cardiac hypertrophy. Mahon¹ has reported two cases of idiopathic hypertrophy of the heart with endocardial fibrosis in young children. In both of them the heart showed marked hypertrophy and, microscopically, severe myocardial fibrosis. Cases of apparently the same condition have been reported in adults by Levy and Rousselot² and by Levy and von Glahn.³

Doane and Skversky⁴ have described a case of massive cardiac hypertrophy in which there were no valvular lesions or other possible causes for enlargement. This was also associated with active fibroplastic proliferation in the myocardium. Reifenstein and Chidsey⁵ have reported a case of cardiac hypertrophy of unknown cause in an 11-year-old school boy.

Engelhardt and Bruno⁶ have reported cases of Fiedler's myocarditis with autopsy findings; one patient lived two years. They stated that the heart showed cardiac hypertrophy with marked fibroplastic changes in the myocardium.

Saphir⁷ has reported an analysis of 240 cases of myocarditis from autopsy material comprising 5,626 cases. This list included cases of both acute and chronic myocarditis and the etiologies embraced subacute bacterial endocarditis, pyemia, rheumatic bronchopneumonia, lobar pneumonia, and isolated Fiedler's myocarditis. Others occurred in association with ulcerative colitis, carcinoma, bronchiectasis, tuberculosis, streptococcic pneumonia, meningococcic meningitis, acute glomerulonephritis, pyelitis, chronic glomerulonephritis, diphtheria, typhoid fever, and influenza. Reference was also made to myocardial changes in measles, mumps, whooping cough, variola, varicella, paratyphoid, and dysentery.

Candel and Wheelock⁸ have reported eleven clinical cases in which they were able to make the diagnosis of acute nonspecific myocarditis by means of symptoms and electrocardiographic changes. The causes of myocarditis in these cases were considered to be tonsillar abscess, lobar pneumonia, primary atypical pneumonia, scarlet fever, gonococcal arthritis, infectious mononucleosis, and typhus fever. One case of acute diffuse myocarditis was discovered, at autopsy, to have been associated with acute suppurative tonsillitis.

Scherf and Boyd⁹ have asserted that with the frequency of acute infectious diseases and miscellaneous infections, there are but few persons who, during a

lifetime, do not have inflammatory myocardial foci. Alterations in the electrocardiogram, asthenia, slight precordial discomfort, and breathlessness occurring shortly after acute infectious diseases should be considered as possible indications of myocarditis.

From the preceding it can be seen that acute myocarditis may follow, or be associated with, a wide variety of diseases of both acute and chronic nature. The cases of chronic myocarditis with cardiac hypertrophy and fibrosis of apparently unknown etiology could be ascribed to many acute or chronic infections that the individual may have had in early life.

Two cases of chronic fibroplastic myocarditis associated with cardiac hypertrophy are presented. The etiology is obscure but might be the result of some unrecognized acute infectious disease which the individuals suffered earlier in life.

CASE REPORTS

CASE 1.—A young woman, 23 years of age, was observed at intervals for seven years before her death. At the time of the initial examination, at the age of 16 years, no history was obtained of rheumatic fever, chorea, pneumonia, typhoid, scarlet fever, diphtheria, or malaria. She had had measles, chicken pox, whooping cough, and occasional attacks of tonsillitis as a child. A year

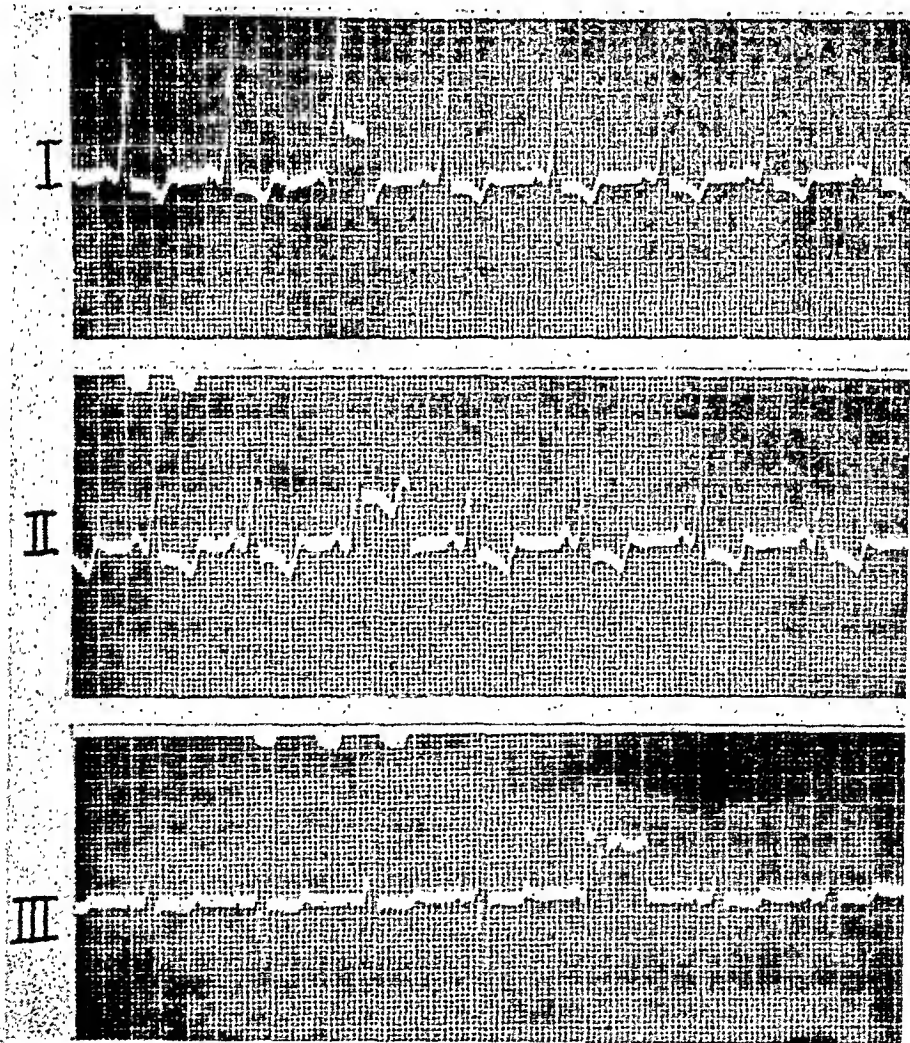


Fig. 1.—Case 1. Dec. 18, 1931.

before she was first seen by one of us (E. R. W.), a heart murmur had been discovered, but there was no history of cardiac symptoms. The family history was unimportant except for severe hypertension in her father. The only pertinent findings on physical examination were a blowing systolic murmur heard in the third and fourth left intercostal spaces close to the sternum, and less intensely at the apex, and an occasional premature contraction. By fluoroscopy, the heart was enlarged to the left without angulation of the left border; on rotation the cardiac shadow impinged on the aorta. No abnormalities were noted in the blood count, urine examination, or Wassermann test. The electrocardiogram showed left bundle branch block (Fig. 1).

The patient was observed frequently. There were no specific complaints or change in her status. Subsequent electrocardiograms showed little change from the original tracing. Shift of body position from the supine to the right and left lateral produced a variation in the height of the QRS complex in Lead I, suggesting no fixation of the heart by pericardial adhesions.

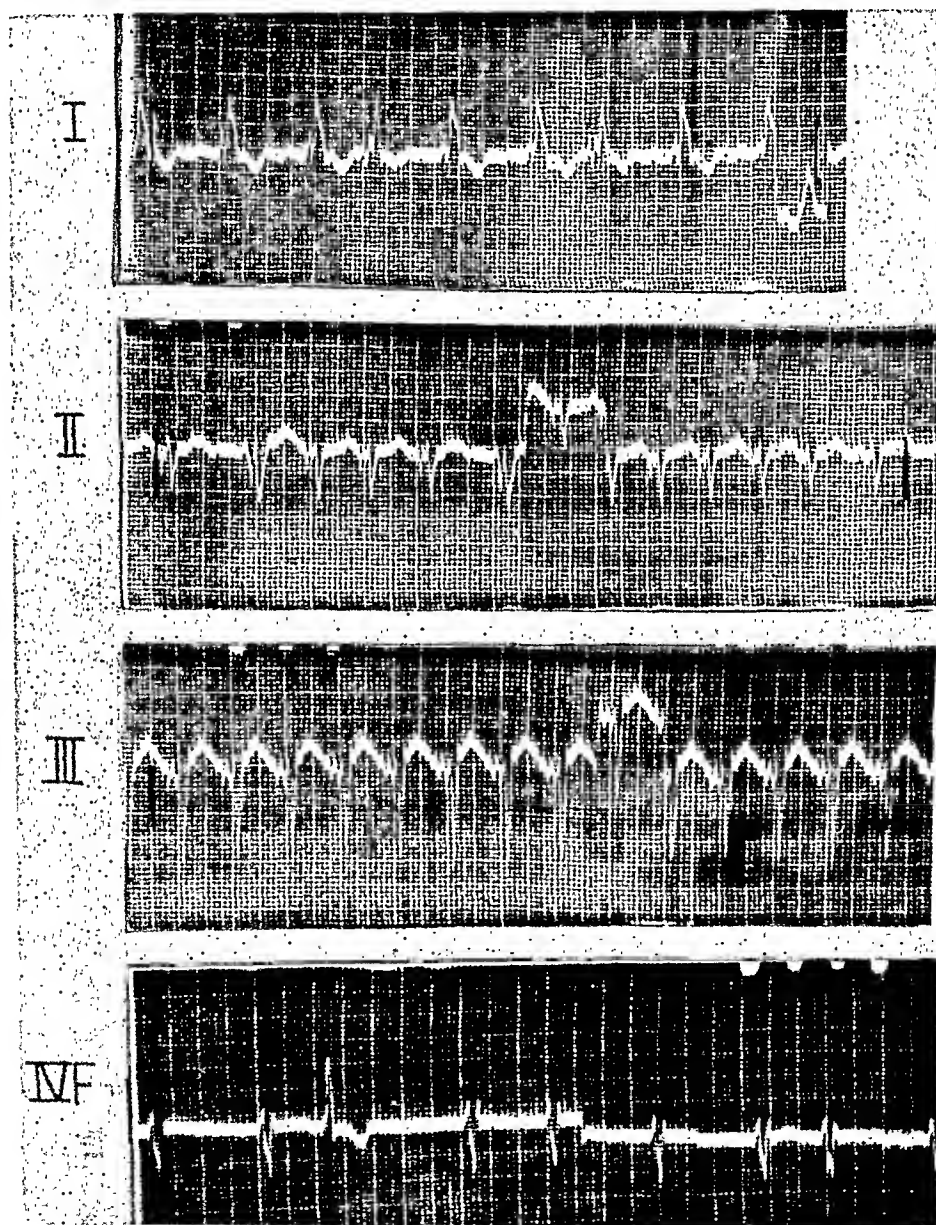


Fig. 2.—Case 1. May 3, 1938.

A month before death, a rapid and irregular heart rate developed, accompanied by moderate fatigue. For several weeks previously she had noted "occasional skips and misses" of the heart-beat and rare spells of tachycardia which had been terminated by right carotid pressure. On examination there were no objective signs of cardiac failure, but the heart rate was very rapid and totally irregular. The apex beat was in the fifth left intercostal space, 11 cm. from the mid-line. There was no thrill or murmur. The blood pressure ranged from 90 to 76 systolic; the

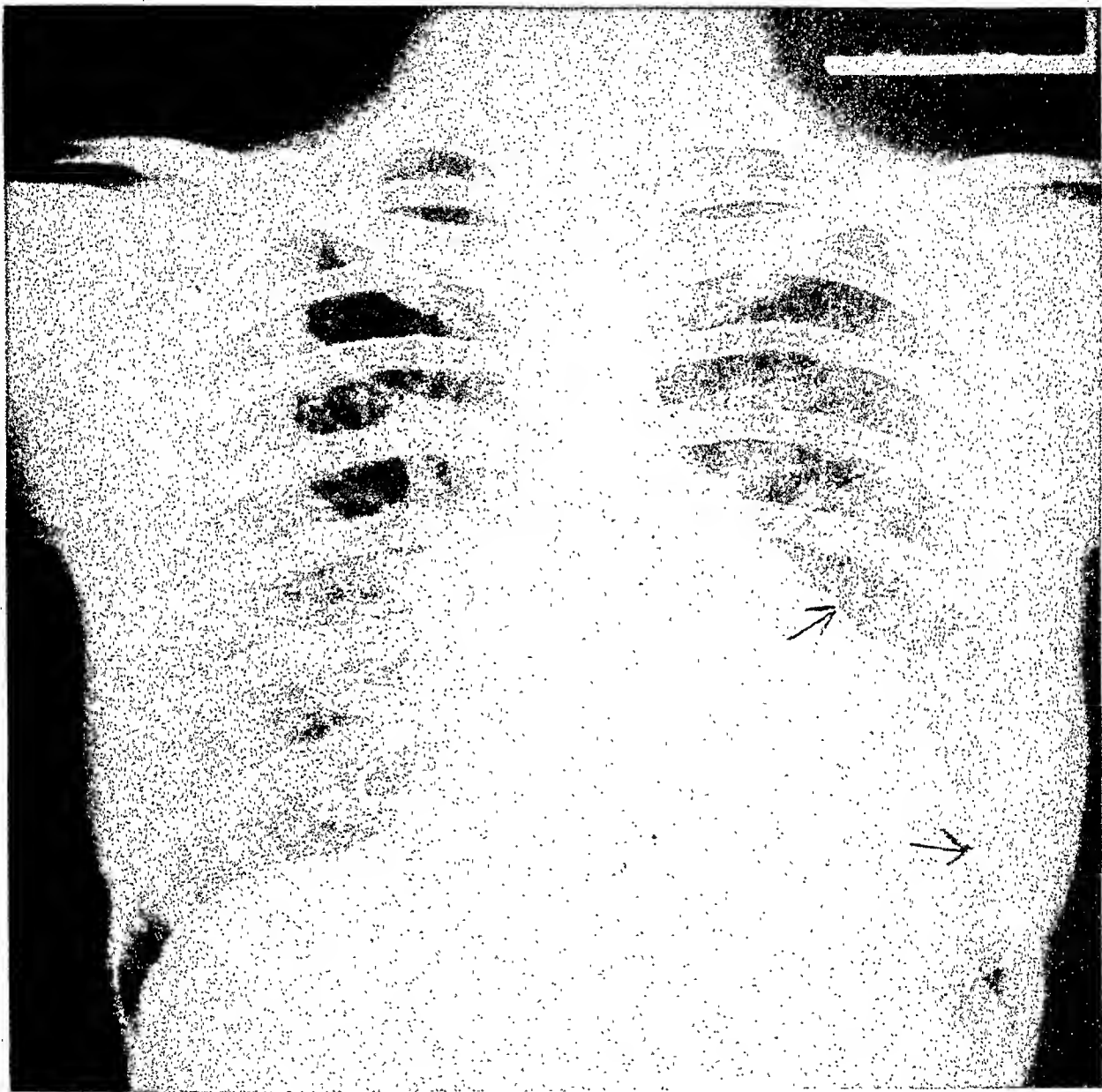


Fig. 3. — Case 1.

diastolic pressure was not obtained. The pulse was small and feeble. There was a considerable pulse deficit. No response was obtained by right or left carotid pressure. The electrocardiogram showed a pronounced change when compared with the tracing made seven years previously. The QRS complexes were wider and splintered and there was absence of R_2 and R_3 which were replaced by deep QS curves. The rhythm was impure flutter with a single premature ventricular contraction (Fig. 2).*

*In portions of the tracing (Fig. 2), pure flutter may be present. In Lead IV F, the mechanism suggests auricular fibrillation.

There was no response to 38 grains of quinidine which produced severe nausea and vomiting. Following digitalis intramuscularly, the heart rate promptly decreased and an electrocardiogram showed auricular fibrillation.

For two weeks the heart remained slow with a reversal to normal rhythm. No murmur could be detected. The second pulmonic was greater than the second aortic sound. The blood pressure was 92/78. X-ray films of the chest were reported to show cardiac enlargement, chiefly of the left ventricle and probably of the left auricle. The aorta was thought to be hypoplastic (Fig. 3).

Some days after leaving the hospital, the patient became acutely ill with severe dyspnea and a rapid, irregular heart rate of 135 to 140 beats per minute. The electrocardiogram showed sinoauricular tachycardia, intraventricular block, and frequent ventricular extrasystoles from a variety of foci. After morphine and digifoline intramuscularly, the heart rate fell to 100 and the patient believed the attack was terminated. Within a few seconds she very suddenly died.

Necropsy Findings.—At autopsy the heart weighed 450 grams. No congenital defects were found. The circumference of the pulmonic valve measured 75 mm.; the circumference of the tricuspid ring, 110 millimeters. The aortic valve measured 62 millimeters. The coronary arteries were patent, and the intima of the vessels was clear. There were a few small fatty changes in the arch and root of the aorta. The left ventricle measured 12 mm. in thickness; the right ventricle, 5 millimeters. The endocardium of the left ventricle was fibrous. On surfaces made by cutting the myocardium there was a marked replacement of the heart muscle by scar tissue. The amount of scar tissue in the ventricle and the septum was most remarkable. The arch, thoracic, and

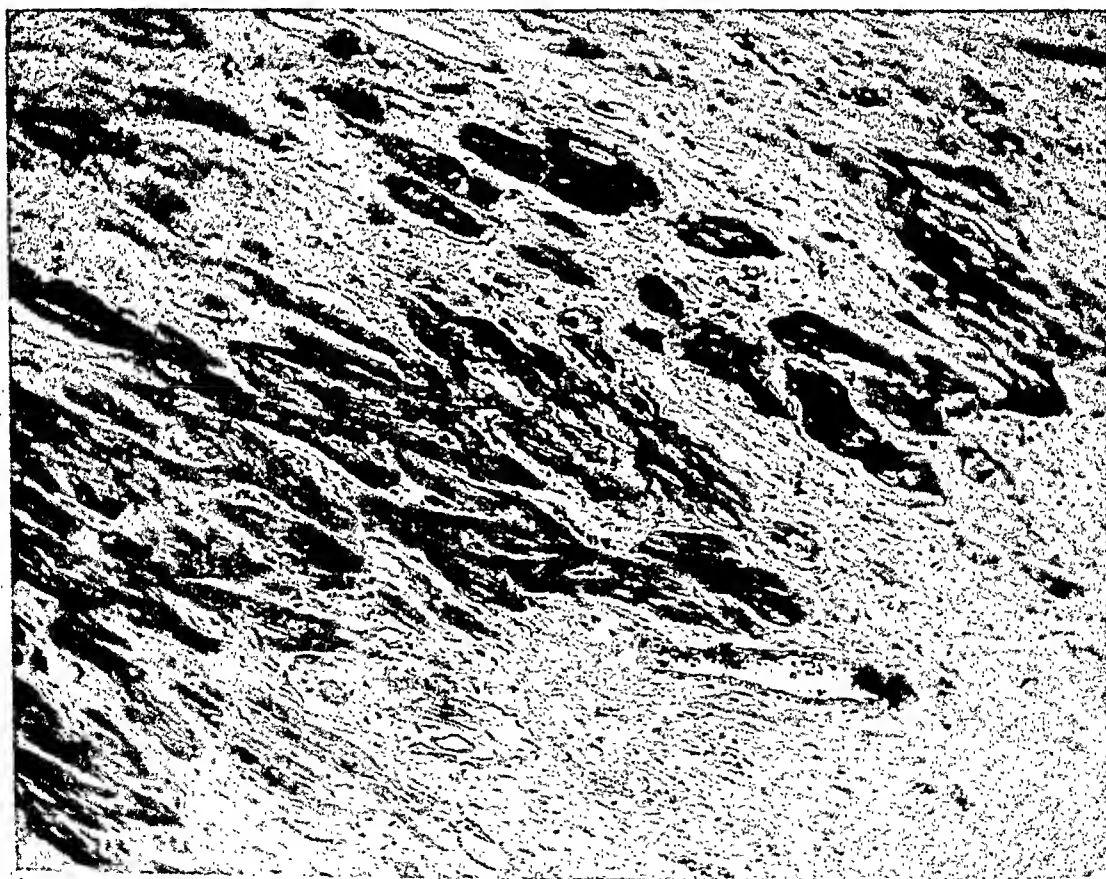


Fig. 4.—Case 1. Section through heart muscle reveals muscle fibers replaced by dense hyalinized connective tissue. The muscle fibers that remain are enlarged and have lost their striations, and the nuclei are pycnotic. There is evidence of vascularization of fibrotic areas. (Hematoxylin and eosin, $\times 120$.)

abdominal portions of the aorta were negative. Microscopically the myocardium was markedly altered (Fig. 4). In many regions the muscle fibers were completely replaced by dense hyaline connective tissue which contained a few fibroblasts. The muscle fibers were pale, granular, and enlarged, and many of the nuclei were in various stages of degeneration. There was a generalized overgrowth of fibrous tissue in the septa separating the muscle bundles. In some places this increase was marked with corresponding atrophy of muscle tissue. There was a moderate infiltration of fat along the fibrous septa. There were no Aschoff bodies or specific inflammatory reactions in the sections studied. The fibrous tissue was most pronounced in the subendocardial areas. Much the same microscopic picture was seen in sections through the wall of both auricles. Culture of heart blood was negative.

A summary of the anatomic diagnosis was (1) marked chronic fibroplastic myocarditis; (2) chronic fibrous pericarditis; (3) hypertrophy of the myocardium of the right ventricle.

CASE 2.—A 23-year-old white woman was apparently perfectly well until two weeks before death, when she developed what she assumed was an ordinary cold. She remained at home in bed and on the following day was somewhat improved. Within the next two days, however, she developed an annoying cough, pain in the left side of the chest, and fever. Two days later a physician made a diagnosis of pneumonia. Following a few days of home treatment with no improvement, she was hospitalized.

On physical examination it was found that the patient was a pale young woman who seemed acutely ill and complained of cough and pains in the chest. The essential findings were confined to the lungs which showed impaired resonance over the left lower lobe with tubular breathing audible over the corresponding area which extended from the axillary region posteriorly to the left base. Over the right base there were also audible definite, coarse, moist râles but no change in the character of the breath sounds, aside from some exaggeration. A clinical diagnosis of lobar pneumonia of the left lower lobe and possible bronchopneumonia of the right lower lobe was made.

An x-ray film of the chest showed a homogeneous density in the left base, consistent with the diagnosis of pneumonia. Blood count showed a leucocytosis of 14,550 with 74 per cent polymorphonuclear cells. Sputum did not type for pneumococcus. Kahn test was negative.

The patient ran a septic temperature while in the hospital and was put on penicillin therapy, oxygen therapy, and glucose and saline intravenously. Her condition remained unchanged the first day, but then she became much worse with a drop in blood pressure to 70/52 and a pulse of 160 beats per minute. There were severe dyspnea and cyanosis. She was given supportive treatment for peripheral circulatory failure but with no response, and she died three days after admission in evident circulatory collapse.

Necropsy Findings.—At autopsy the heart weighed 545 grams. All of the chambers were markedly dilated. The left ventricular wall measured 23 millimeters. The circumference of the aortic ring measured 63 mm.; that of the pulmonary ring, 60 millimeters. The coronary arteries were smooth and patent but very small, measuring 3 to 5 mm. in circumference. The endocardium of the ventricles was everywhere fibrotic. The myocardium was firm and grayish-purple in color, and, on section through the wall of the ventricle and the interventricular septum, there were patchy areas of grayish-white which cut with increased resistance. Microscopic section of the myocardium (Fig. 5) revealed a diffuse patchy fibrosis throughout. In some areas, especially in the endocardium, this was more extensive than in others. The fibrous tissue was of a dense hyalinized type and relatively acellular. The muscle cells, which were not involved by the fibrosing process, were greatly hypertrophied and were somewhat granular. The nuclei appeared swollen and many of them were squared. The striations were diminished and many of the muscle cells were vacuolated and fragmented. There were various degrees of degeneration in the muscle cells; in some places this amounted to complete replacement by fibrous tissue. In some areas there were occasional round cell infiltrations. In others there were focal accumulations of plasma cells and round cells. None of these were typical Aschoff bodies. In none of the sections was

there any evidence of a recent inflammatory process. The epicardium was slightly thickened and fibrotic and moderately infiltrated with round cells. The lungs showed a severe bronchopneumonia and interstitial pneumonia.

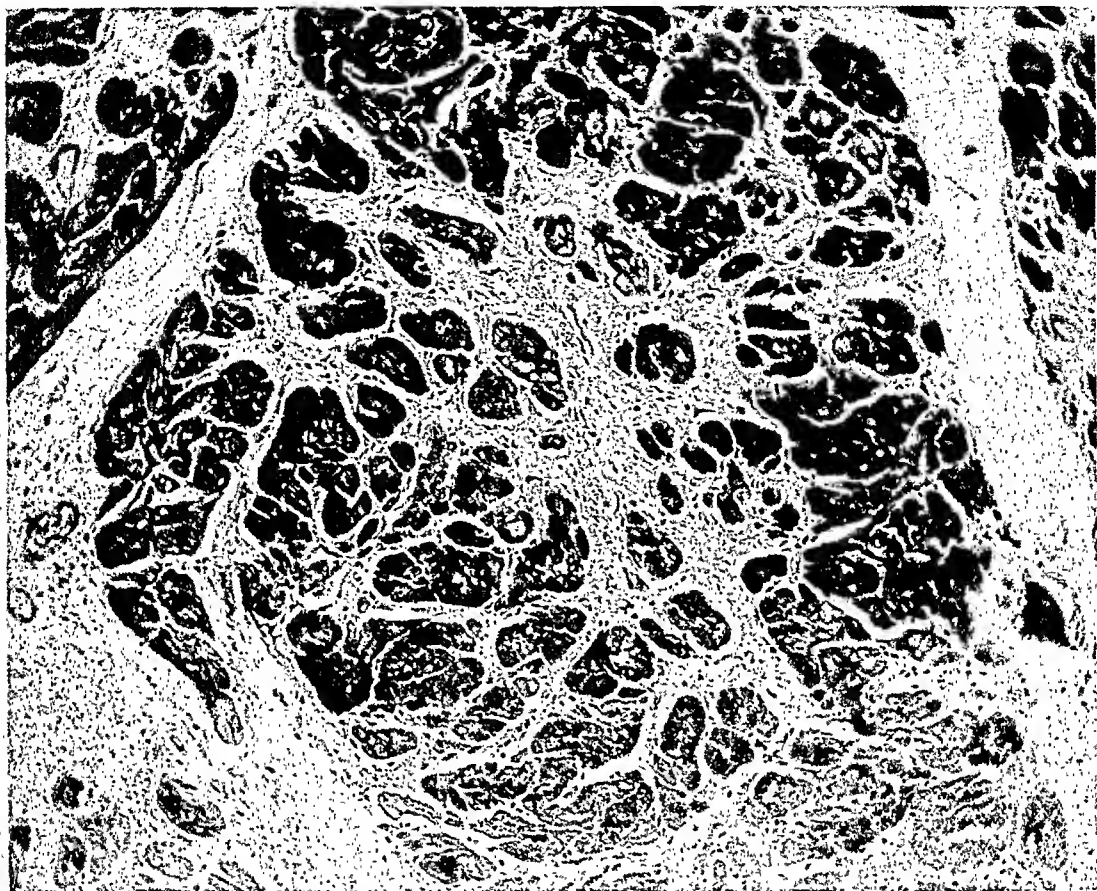


Fig. 5.—Case 2. Section through heart muscle reveals muscle bundles being replaced by dense hyalinized fibrous tissue. There is some round cell infiltration between the muscle bundles and into the fibrous tissue. The muscle fibers are enlarged and their nuclei are squared. The striations are barely visible, and some of the cells are vacuolated. (Hematoxylin and eosin, $\times 120$.)

The anatomic diagnosis was (1) marked chronic fibroplastic myocarditis; (2) bronchopneumonia and interstitial pneumonia of the left lower, left upper, right lower, and middle lobes of the lungs.

COMMENT

Two cases of chronic fibroplastic myocarditis associated with cardiac hypertrophy have been described. Both cases were in young women and the exact cause of the underlying pathology is obscure. In Case 1, the cause of death was the eventual failure of the diseased heart. In Case 2, death was caused by intercurrent pulmonary infection. The two hearts were practically identical, grossly and microscopically, and showed cardiac hypertrophy and fibrosis. We believe the distinctive pathology in these cases represents the healed end result of a previously existing acute myocarditis, or Fiedler's myocarditis, which may have been the result of some former acute illness.

CONCLUSIONS

1. Two cases of chronic fibroplastic myocarditis associated with cardiac hypertrophy are presented. The etiology of the myocarditis is obscure but was probably associated with some acute infectious disease earlier in life.

2. A review of the literature reveals that myocardial involvement in the course of an acute infectious disease is more frequent than was formerly supposed and that careful evaluation and electrocardiographic investigation during the course of an acute infectious disease will reveal many more cases of cardiac involvement.

3. Numerous cases of chronic myocarditis have been reported in the literature in which the etiology can be traced to some acute or chronic infectious disease.

ADDENDUM

Since the preparation of this article, Sellers and Phillips¹⁰ have described two fatal cases of a similar nature in young individuals. They also suggest a like etiology for the diffuse myocardial fibrosis.

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SINGLE CORONARY ARTERY

CASE REPORT OF AN ABSENT RIGHT CORONARY ARTERY

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ANOMALIES in size and distribution of the coronary arteries are fairly common but complete absence of one or the other of the main arteries is rare. In a study of the literature accompanying their report of a case, Krumbhaar and Ehrich¹ in 1938 found only five cases of absent right coronary artery that satisfied Hyrtle's postulate.² This postulate requires that one artery supply

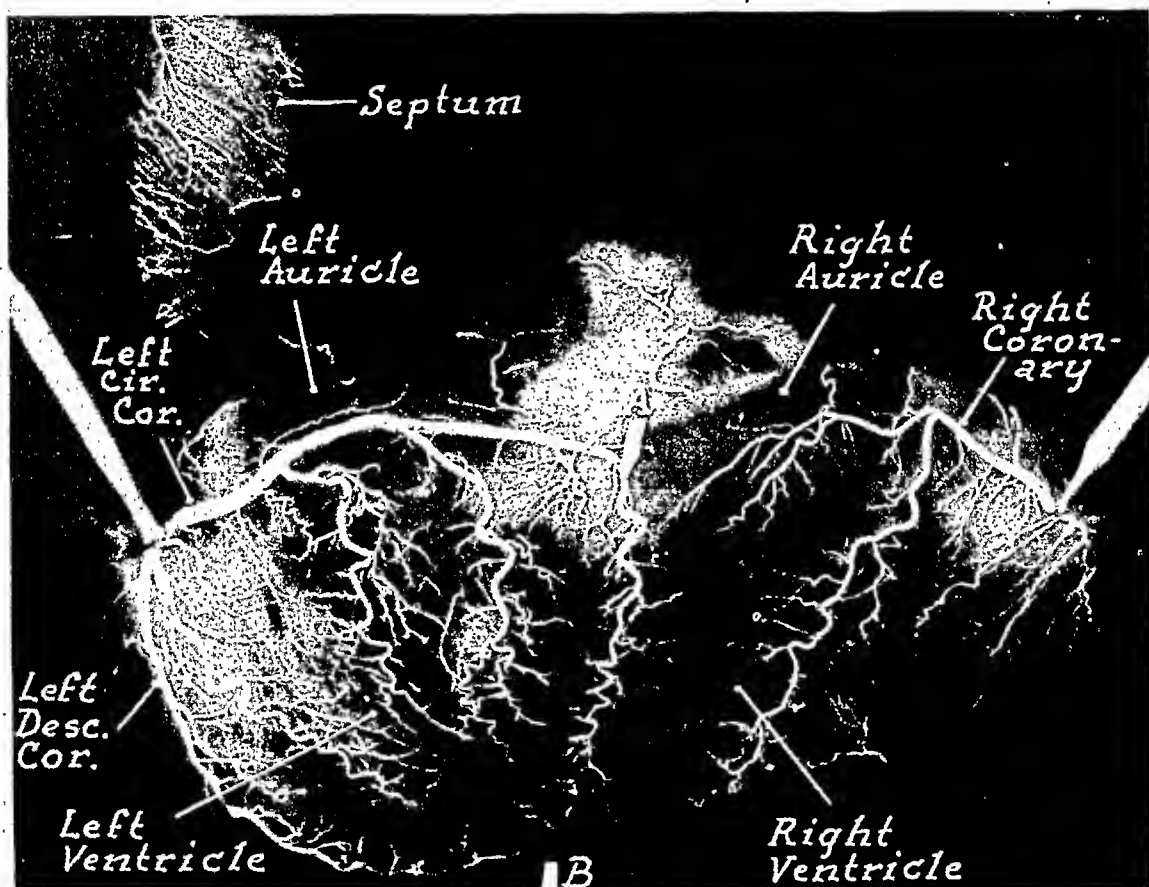


Fig. 1.—Roentgenogram of a normal arterial system following post-mortem injection. The specimen is opened and unrolled according to the Schlesinger technique³ to bring the arteries into the same plane. A and B indicate the position of the posterior border of the interventricular septum which has been dissected out and placed in the upper right-hand corner. The posterior descending branch of the left circumflex is visible in the area between A and B.

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the whole heart and the anomaly must not be a matter of a common aortic orifice of the two arteries or an unusual origin of the missing one; that is, a misplaced anlage. Our purpose is to report another case of absent right coronary artery, the first in which a roentgenogram of the remaining coronary artery was obtained after its post-mortem injection with a radiopaque substance.

CASE REPORT

A 66-year-old white woman was admitted to Colorado General Hospital on Aug. 24, 1942, complaining of severe abdominal pain, abdominal swelling, and vomiting of one month's duration. The past history was significant only for previous surgical removal of both Fallopian tubes and an ovary. Physical examination revealed abdominal tenderness, distention, and tympanitic resonance. The blood pressure was 160/90. A diagnosis of intestinal obstruction was made and the patient was treated by Wangenstein suction drainage, intravenous fluids, and supportive measures. Temporarily the response was good but after ten days, the abdominal distention recurred and laparotomy was performed on Sept. 4, 1942. Carcinomatous obstruction was discovered in the sigmoid region of the large intestine and cecostomy only was performed. The postoperative course was satisfactory until Sept. 18, 1942, when the patient suffered a sudden attack of dyspnea, loss of consciousness, and fall in blood pressure. Death occurred twenty minutes later.

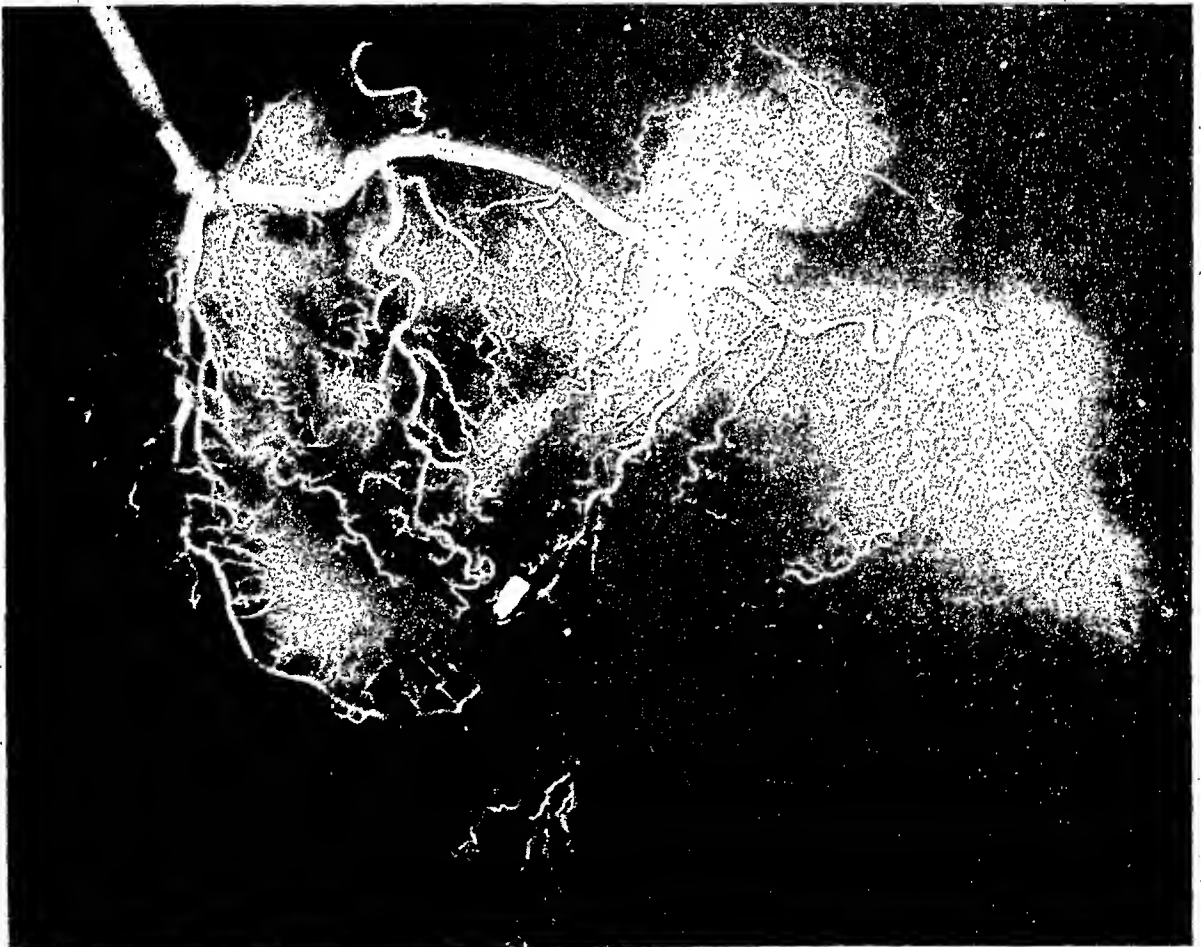


Fig. 2.—Roentgenogram of the arterial system with an absent right coronary artery. Note the continuation of the left circumflex artery beyond the posterior descending branch to supply all of the right ventricle. Interventricular septum below main specimen.

Necropsy Report.—The significant extracardiac findings were (1) an annular carcinoma in the sigmoid region of the large intestine with perforation and secondary pelvic abscess and (2) a large embolism involving the right pulmonary artery and its branches.

The heart weighed 340 grams. It was slightly enlarged but of normal shape and appearance. The tricuspid and mitral valves were slightly thickened along their free margins and the chordae tendineae and papillary muscles of the mitral valve were somewhat enlarged. The aortic valve showed a ringlike sclerosis of the bases of the cusps and, in addition, the posterior cusp was thickened by small calcified plaques. Microscopic examination of the heart revealed moderate to marked arteriosclerosis in vessels of all sizes. The largest arteries showed intimal thickening and infiltration by foam cells. In some fields the intima also showed crystalline deposits and calcification. Perivascular round-cell infiltration was present about the adventitial vasa vasorum. The medium- and small-sized arteries displayed intimal hyaline thickening and hyaline changes also in the other layers. The myocardium in both ventricles showed scattered areas of fibrosis in which atrophic myocardial fibers, round cells, fibroblasts, and pigment were apparent.

Post-Mortem Injection and Roentgenography of Coronary Arteries.—Only one coronary arterial orifice was found; it opened into the left anterior aortic sinus. This artery was injected and the specimen unrolled and radiographed according to the Schlesinger technique.³ Fig. 1 shows the roentgenogram of a normal control with the coronary arteries and the various parts of the heart labelled. Fig. 2 is the roentgenogram of the case reported here. The right coronary artery was absent and its place and distribution were taken over by the circumflex branch of the left coronary artery. Instead of terminating in the posterior descending branch, as occurred in the normal in Fig. 1, the circumflex branch continued in the atrioventricular sulcus and supplied all of the right ventricle. Moderate distortion of the large arterial branches due to sclerosis was noted, but the lumens were not occluded at any point.

SUMMARY

A case of absent right coronary artery is reported in which post-mortem injection and roentgenography of the coronary arteries were performed.

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Abstracts and Reviews

Selected Abstracts

Mayock, R. L., Koop, C. E., Riegel, C., Kough, N. T., and Starr, I.: Convalescence from Surgical Procedures. III. The Relation of Nitrogen Balance and Blood Volume to Abnormalities of the Circulation. *Am. J. M. Sc.* 212:591 (Nov.), 1946.

The purpose of this investigation was to discover whether patients whose stores of nitrogen were maintained by special methods of feeding before or after operation were in reality in better condition than those who developed a negative nitrogen balance. The clinical impression of the surgeons that such was the case was confirmed by objective studies. Postoperative abnormalities noted in the ballistocardiogram occurred far more frequently in those in negative than in those in positive nitrogen balance, and the latter required a shorter average period of hospitalization than the former.

Interesting data were obtained concerning the relation of blood volume to the circulation, since a positive correlation existed between blood volume and cardiac output per minute. This is consistent with the view that the filling of the heart was improved by the increased amount of blood. Equally interesting was the relation between blood volume and abnormal ballistocardiograms, for the most abnormal types of ballistocardiograms occurred most frequently in patients with unusually small blood volumes. Poor cardiac filling may be responsible for these abnormalities since it has been shown that in some patients with obvious heart disease the abnormalities of form occur only in that part of the respiratory cycle in which cardiac filling is the poorest. Patients with biliary tract disease showed a pronounced tendency to have subnormal circulations before operation and to develop abnormal ballistocardiograms after operation.

DURANT.

Priest, W. S., and McGee, C. S.: Streptomycin in the Treatment of Subacute Bacterial Endocarditis. *J. A. M. A.* 132:124 (Sept.), 1946.

In the treatment of subacute bacterial endocarditis with penicillin, four organisms were encountered by these authors which were highly or completely resistant to penicillin. One of these was the *Hemophilus parainfluenzae*; the other three organisms were strains of streptococci. The *Hemophilus parainfluenzae* was apparently unaffected after many weeks of penicillin therapy in daily dosage up to 2 million units. Sulfamerazine alone also had no apparent effect in vivo. Cure resulted from the combined administration of penicillin in daily dosage of 500,000 to 1,000,000 units and sulfamerazine in dosage to raise the level of the drug in the blood to 0.8 to 11 mg. per cubic centimeter. The organism in this case was subsequently found to be sensitive in vitro to streptomycin.

In a group of thirty-four patients, three strains of streptococci were encountered which were highly insensitive to penicillin. One was typically *Streptococcus viridans* after freezing, but was rather atypical in primary cultures of blood. The other two were typical nonhemolytic streptococci. The vitro sensitivity to penicillin ranged from 0.8 to 6 units per cubic centimeter. Sensitivity to streptomycin ranged from 0.1 to 1 unit per cubic centimeter. Streptomycin

apparently produced sterilization of the valvular lesions in Case 1, resulted in negative cultures of blood after penicillin therapy had failed in Case 2, and was solely responsible for the cure obtained in Case 3.

The dose of streptomycin used, 500,000 units (0.5 Gm.) per day, is not necessarily that which will be adequate in all cases in which the use of the drug is indicated.

BELLET.

Ramos, G. J., and Peralta, R.: *Effects of Quinidine on the Circulatory System.* Arch. Cardiol. Mex. 16:302 (July), 1946.

The effect of small doses of quinidine on cats under dial anesthesia was studied. The heart rate, electrocardiogram, blood pressure, cardiac and vascular responses to central stimulation of the vagus and of the sciatic nerves, to temporary closure of both carotid arteries, and to epinephrine were investigated.

The effects of small doses of quinidine (0.25 mg. to 1.0 mg. per kilogram) were as follows: (1) The speed of recovery of the conducting system was decreased; this was shown by prolongation of the P-R interval whenever tachycardia was present. (2) The excitability of the myocardium was decreased in response to electrical stimulation or epinephrine injection. (3) The heart rate was decreased. Larger doses (1 to 5 mg. per kilogram) yielded similar but far more striking results: Prolongation of the P-R interval, even with a normal heart rate, decreased response of the heart to epinephrine, and to stimulation of the vagus nerve. Still larger doses (5 to 10 mg. per kilogram) resulted in a reduction of the blood pressure and a depression of the respiratory center.

LUISADA.

Levine, H. D., and Erlanger, H.: *Atabrine and the Electrocardiogram.* Am.J.M.Sc. 212:538 (Nov.), 1946.

In a series of 179 individuals, atabrine in therapeutic and suppressive doses had no significant effect on the electrocardiogram. It is concluded that abnormalities previously reported as occurring in patients taking atabrine can be attributed to other causes.

DURANT.

Patek, A. J., Jr., Kendall, F. E., Victor, J., Lowell, A., Coleher, H., and Seegal, D.: *Venous Thrombosis After Infusion With Gelatin Solutions Containing Mercurial Preservatives.* Am.J.M.Sc. 212:561 (Nov.), 1946.

Gelatin solutions containing phenyl mercuric borate or merthiolate as preservatives were injected eighty times into thirty-nine patients, usually in amounts of 1,000 cubic centimeters. Local thrombosis occurred in twenty-seven of the eighty veins injected. Venous thrombosis did not occur, however, when gelatin solutions free of mercurial preservatives were injected. Similar results were obtained in experimental studies using ear veins of rabbits. The addition of sodium thiosulfate or methionine to gelatin solutions containing phenyl mercuric borate appeared to give partial protection against the thrombotic action of this mercurial preservative. It is postulated that this converts the mercuric ions to the mercurous form and in this way renders the compound less irritative to the vein.

DURANT.

Stein, I.: *Postural Heart Block.* Am.J.M.Sc. 212:604 (Nov.), 1946.

Two cases of alteration in the A-V conduction time resulting from change in posture are described. In one of these, complete heart block was present in the recumbent position, but lesser degrees of block were present when the patient was upright. The other patient presented a second degree heart block while supine and a first degree in the standing position. The block was caused by digitalis. Because both patients showed reduction of the block in response to atropine, vagal

action was assumed to be responsible for the findings. It is recommended that all patients with A-V conduction disturbances be studied in several postures for more complete evaluation of the clinical and electrocardiographic pictures.

DURANT.

Taquini, A. C., and Lozada, B. B.: The Clinical Diagnosis of Tricuspid Valvular Lesions. *Medicina* 6:561, 1946.

An analysis of the symptoms and signs observed in fifteen patients with tricuspid valvular lesions led to the following conclusions: Dyspnea was the primary symptom in 14 patients, and appeared many years prior to other symptoms or signs of circulatory insufficiency. The color of the skin was normal in only one of the fifteen patients; eight had cyanosis and six of these were also slightly jaundiced. Venous congestion was present in every patient of the series. The venous pulse was the most significant diagnostic factor. Liver pulsation and a "balanced" thoracic movement were detected in thirteen instances. Twelve patients showed edema at some time: nine of these were ascitic, and three had hydrothorax. The auscultatory signs were not of great diagnostic value. The diagnosis could in many instances be confirmed by x-ray; the most significant findings in fluoroscopy and kymography were the positive systolic beating of the right auricle and vena cava, and the systolic elevation of the right hemidiaphragm.

MALINOW.

Horrax, G.: Experiences With Cortical Excisions for the Relief of Intractable Pain in the Extremities. *Surgery* 20:593 (Nov.), 1946.

The results following excision of postcentral cortex for the relief of painful extremities in four patients are presented. In the two patients with causalgia and phantom limb pain, the cortical excisions were followed by transient relief only. In the two patients who had central pain, relief was complete in one during the remainder of his life (ten months); in the other, relief had been complete in the contralateral leg (one year and ten weeks, postoperatively) and was complete in the hand and arm for five months following the excision. Certain features concerned with sensory responses to cortical stimulation and sensory deficits following postcentral cortical excisions are discussed.

NAIDE.

Elkin, D. C., and Harris, M. H.: Arteriovenous Aneurysm of the Vertebral Vessels. *Ann. Surg.* 124:934 (Nov.), 1946.

Of 500 operations performed for arteriovenous fistulae and aneurysms, ten were on arteriovenous fistulae of the vertebral vessels in their cervical or extracranial course. These ten cases are reported in detail with a review of the anatomy of the vessels, the diagnosis of the lesion and with suggested operative methods of approach and treatment.

Of all the aneurysms and fistulae in the body, the diagnosis of those of the vertebral vessels is the most difficult to make. It was made with certainty in only five patients in this series, although it was suspected in others. It is likely to be confused with more common lesions in this region, particularly fistulae between the internal jugular vein and branches of the external carotid artery. It may also be confused with fistulae arising from other branches of the subclavian artery, particularly the inferior thyroid, the transverse scapular and transverse cervical vessels. Since the common carotid lies moderately superficial in the neck where it can be occluded by digital pressure, the bruit of fistulae arising from branches of this vessel are usually obliterated with ease. If the bruit does not disappear on compression of the common carotid artery, the vertebral vessels should be suspected as the site of the lesion. Since the vertebral vessels lie deep in the neck, obliteration of the bruit is difficult to obtain by pressure.

NAIDE.

Mangun, G., and Myers, V. C.: Cardiac Muscle: Further Studies: Investigation of Chemical Changes in Myocardial Insufficiency With Special Reference to Adenosinetriphosphate. Arch. Int. Med. 78:441 (Oct.), 1946.

The authors found that creatine, total phosphorus, acid soluble phosphorus, and potassium are decreased consistently in chemical studies of the muscle of the failing heart. One of the authors found also that in the late stages of cardiac failure in dogs with aortic insufficiency there was a marked decrease in the adenosinetriphosphate and phosphorus content of the left ventricle. In order to study this phenomenon in the human heart, the authors devised a technique compatible with the fact that adenosinetriphosphate and related compounds break down rapidly after death. The method consisted essentially in the precipitation of purines in hydrolyzed trichloroacetic acid extract of tissue with copper bisulfite and the estimation of the nitrogen content of the precipitate and conversion of unchanged adenosinetriphosphate purines to oxypurines. The left ventricle, right ventricle, and skeletal muscle of twenty-four specimens were examined at autopsy. Of the twenty-four patients, six had died of cardiac failure, five of tuberculosis, eight of pneumonia, and five of miscellaneous conditions. The results showed that the acid-extractable purine content of the left ventricle calculated as adenine is decreased in myocardial insufficiency. Lower concentrations of purine were also observed in the myocardium of the right ventricle in some but not all cases of pneumonia.

HORWITZ

Cooper, W. M.: Clinical Evaluation of Sotradecol, A Sodium Alkyl Sulfate Solution, In The Injection Therapy Of Varicose Veins. Surg., Gynec. & Obst. 83:647 (Nov.), 1946.

The sclerosing therapy of varices has its limitations. One reason why it has recently fallen in disrepute is that the agents used were not adequate and had to be used in ineffective doses to avoid grave sequelae. The author reports the use of sodium tetradecyl sulfate solutions on 327 patients who received 2,064 injections in varicose veins with and without ligation of the saphenous vein and its tributaries. The experience with this sclerosing agent indicates that a substantial improvement of sclerosing therapy has been made possible with this new agent. It was found to be two to four times more effective than soap solutions. Its action appeared to be stronger and less diffuse. Side effects such as pain, cramps, sloughing, skin eruptions, and systemic reactions occurred much less frequently than with other sclerosing agents. The pharmacology of this compound is discussed and compared with agents used previously.

NAIDE

Wybauw, M.: The Amount of Vitamin B₁ In The Urine of Cardiovascular Patients Who Do Not Present a Frank Syndrome of Avitaminosis or of Hypovitaminosis But Are Nevertheless Clinically Improved by the Administration of This Vitamin (B₁). Acta Cardiologica 1:18, 1946.

The author studied a series of cardiac patients who showed no evidence of avitaminosis but were nevertheless improved symptomatically by administration of vitamin B₁. A dose of 2 mg. of vitamin B₁ was given to each patient. It was found that 16 to 29 per cent of the absorbed dose was excreted in the urine. This observation is regarded as further evidence that the improvement brought about by vitamin B₁ administration in cardiac patients is not contingent on the existence of avitaminosis.

LAPLACE.

Goldblum, A., and Segall, H. N.: Progress Report on a Case of Auricular Fibrillation Demonstrated in an Infant of Three Months. Canad. M. A. J. 55:501 (Nov.), 1946.

In 1935 the authors made observations on a 3-month-old infant who had auricular fibrillation which probably had been present since birth. They were not able to find any report in the literature of a similar case. Neither quinidine nor digitalis therapy had any effect on the auricular rhythm which became normal spontaneously when the child was about 1 year old. The child

was next seen at the age of 9. A physical examination revealed essentially normal cardiac findings. The heart was normal in size and shape by roentgen study and the electrocardiogram was normal. Final examination was made in 1946 at the age of 11, at which time cardiac findings were also essentially normal.

BELLET.

Quintin, T. J.: Complete Heart Block in Pregnancy (Report of Two Successful Deliveries). *Canad. M. A. J.* 55:600 (Dec.), 1946.

Quintin adds to the literature the report of another patient with complete heart block who satisfactorily withstood the strain of pregnancy and delivery. Up to 1938, Jensen had found only 14 such cases recorded in the literature. Most of the patients in whom complete heart block complicated pregnancy were delivered by cesarean section. In the patient reported by the author, two pregnancies were terminated by normal deliveries. The patient was 27 years of age during her first pregnancy and 29 years in her second. The electrocardiogram showed complete A-V heart block with a ventricular rate of 34 per minute. There was no evidence of cardiac embarrassment during pregnancy and the deliveries were uneventful.

BELLET.

Selye, F. L.: The Absorption of Enteric Coated Ammonium Chloride. *Canad. M. A. J.*, 55:45 (Nov.), 1946.

This author reports the not infrequent failure of enteric-coated tablets of ammonium chloride to be absorbed from the gastrointestinal tract. These may be observed as opaque particles by x-ray. In many instances in healthy young adults, prolonged administration of such tablets resulted in no acidosis, although the tablets were destroyed before excretion, presumably at a level too low in the gastrointestinal tract to allow absorption. He feels that the absorption of enteric-coated tablets is at best unpredictable. He later used ammonium chloride heavily coated with gelatin and observed gastric discomfort in only two of sixty cases; absorption occurred in all cases.

BELLET.

Ochsner, A.: Venous Thrombosis. *J. A. M. A.* 132:827 (Dec. 7), 1946.

Clinical experience and experimental observation have shown that there are two types of venous thrombosis which differ etiologically, symptomatically, prognostically, and therapeutically. Thrombophlebitis consists of an inflammatory process associated with thrombosis, whereas phlebothrombosis may be defined as partial or complete venous occlusion by an intravascular clot which is unassociated with inflammation, the clot being loosely attached to the vein wall. In thrombophlebitis the femoral and iliac veins are usually the vessels involved. Since the thrombosis in thrombophlebitis is the result of inflammatory change in the vein wall, particularly the endothelium, the resulting clot is either a white or mixed thrombus and is firmly attached to the vein wall. For this reason, thrombophlebitis is, except in rare instances, not associated with embolism because the clot is attached and cannot become detached. In contrast, the mechanism of the formation of the thrombus in phlebothrombosis is entirely different. There is no inflammatory process in the vein wall and the clot is the result of two factors: the increased coagulability of the blood and the slowing of the blood stream. These thrombi usually originate in the veins of the calf muscles or in the veins of the plantar aspect of the foot, but may extend up into the deep veins of the thigh or pelvis. Because the clots are not firmly attached, portions of them frequently are carried through the venous system to the heart and lungs, and produce various grades of pulmonary infarction. It has been shown that 92 per cent of the patients with postoperative venous thrombosis and primary acute thrombophlebitis had hypercoagulability of the blood and that the average acceleration of blood coagulation in these patients was four and one-half times that in normal subjects.

In most cases of thrombophlebitis the clinical picture is definite and well defined. The patient complains of pain, fever and, usually, swelling of the extremity. Color changes and a lowering of the temperature of the extremity are often observed. In superficial vein involvement, the skin

overlying the affected vein is red and warm. The patient with phlebothrombosis is likely to have no symptoms whatever. This author is convinced that the diagnosis of phlebothrombosis must be made before any symptoms are manifest, because usually the symptoms are the result of a complication such as infarction or a beginning inflammatory process *resulting* from the retained thrombus. These patients do not usually have fever, but the erythrocyte sedimentation rate is usually increased and a positive Homan's sign should be looked for in all patients who are in bed and who have had tissue injury. This author believes that phlebography is unnecessary and that at the slightest sign of the condition immediate therapy should be instituted, before the clot has a chance to become detached.

The prognosis in thrombophlebitis as regards life is good, but unless adequate therapy is instituted, post-phlebotic sequelae, such as edema, pain, ulceration and streptococcic infection, are likely to develop. On the other hand, the patient with phlebothrombosis, although apparently not ill, is a potential fatality. The treatment of uncomplicated thrombophlebitis is conservative and consists of vasodilatation accomplished by anesthetizing the regional sympathetic ganglions. Only in rare cases of suppurative thrombophlebitis is radical therapy necessary; this consists of venous ligation proximal to the site of suppurative thrombophlebitis.

Phlebothrombosis, because of the great likelihood that the clot will become detached and produce pulmonary infarction or massive occlusion of the pulmonary artery which will cause sudden death, should be treated without delay by means of venous ligation or thrombectomy. Anti-coagulant therapy may be used prophylactically in persons known to have a thrombosing tendency; in the treatment of phlebothrombosis it will prevent the formation of additional thrombi but will not prevent the detachment of the thrombus which already exists.

BELLET.

Stein, I.: A Study of Abnormal T Waves in Patients Presenting no Evidence of Organic Heart Disease. J. Lab. & Clin. Med. 31:837 (Aug.), 1946.

Among 5,520 electrocardiograms made on 4,810 patients in the recumbent position at a large Army regional hospital, 51 or 1.0 per cent of this total showed evidences of abnormality of the T wave despite the absence of other criteria of heart disease. Bizarre T waves were confined to the chest leads in 23 of these, and in 28 they appeared in the limb leads. The subjects varied from 19 to 47 years and were of both sexes. The average age was 30, and the constitutional type varied widely between sthenic and the asthenic, the majority being, however, of medium build. A majority of the patients who showed this change in the T wave were psychoneurotic and presented symptoms referable to the cardiovascular system which could readily have been catalogued under the diagnosis of neurocirculatory asthenia. In 43 of 50 patients who showed the abnormal T wave, standard exercise tests converted the bizarre T wave to normal. The author discusses the possible underlying causes for the abnormality of the ventricular deflection and agrees with the conclusion of other writers that secondary imbalance of the autonomic nervous system is probably responsible for the changes.

WENDKOS.

Schwartz, B. M., McIlroy, G. H., and Warren, H. A.: Acute Mediastinal Emphysema. Ann. Int. Med., 25:663, (Oct.), 1946.

Seven cases of acute mediastinal emphysema are discussed in some detail. The resemblance of some of the clinical features of this condition to angina pectoris, acute coronary thrombosis, and acute pericarditis are emphasized. In six of the cases, the etiology was not apparent; one was apparently caused by an acute respiratory infection associated with bronchial asthma. The mechanism responsible for acute mediastinal emphysema is briefly reviewed. The recurrent nature of the condition is stressed, in view of the experience with the seven cases reported in this paper. The association of pneumothorax is also emphasized and the authors indicate the desirability of making a careful examination of the precordial region for the physical signs of mediastinal emphysema in all cases with a small left apical pneumothorax. The most satisfactory treatment,

in their experience, consisted of prolonged bed rest. In all of the cases reported in this paper, the characteristic crackling sounds of mediastinal emphysema were heard, and for this reason the importance of this diagnostic sign is stressed by these authors.

WENDKOS.

Andreyev, S. V., Borisova, E. I., and Rusinov, V. S.: Direct Electrocardiography of Heart During Restoration (Resuscitation of the Isolated Human Heart). Am. Rev. Soviet Med. 4:4 (Oct.), 1946.

These authors recorded their observations on 100 isolated hearts obtained from children who had succumbed to various infections. The hearts were perfused with a modified oxygenated Tyrode solution. The experiments were started seven to thirty-six hours after death. In children up to 5 years of age the heart retains conductivity in situ up to thirty-six hours. Usually a series of premonitory signs are observed before normal contractility is resumed. These are: contraction of the aorta, response of the heart to mechanical stimulation, and fibrillation and flutter of the auricles. At the onset of revival, contractions of the cadaver heart are very weak, hardly noticeable, and the rate is slow, 20 to 25 per minute. There is no definite localization of the first foci of contraction, usually these foci are first observed in the right or left auricular appendage or in other parts of the auricles. With three or more foci of excitation, each governed by its own rhythm, the resulting graph of the composite action of the independent foci is a picture of fibrillation. When there are a total of five to six foci of contraction in both auricles, the resulting rhythm is auricular fibrillation with an auricular rate exceeding 300 per minute.

As a result of electrophysiologic observations on the cadaver heart during the restoration of its function, these authors conclude that fibrillation of the human heart is dependent on the appearance of a number of foci of excitation, each one of which initiates its independent rhythm.

In applying the lead electrodes directly to the right ventricle, the initial complex of the tracing has a small R wave directed upward without a preliminary Q wave and a long S wave directed downward. In applying the electrodes to the surface of the left ventricle, the R wave is preceded by a Q wave. They therefore obtain a graph identical with the initial complexes of partial electrocardiograms obtained separately from the right and left ventricles by Groedel.

They suggest that this method should prove valuable in the investigation of many other problems in electrocardiography.

BELLET.

Hirsch, S.: Localized Amyloidosis Resembling Arteriosclerosis of the Heart, Cardiologia 10:280, 1946.

The small branches of the coronary arteries, unlike the vessels of other organs, show no hyalinization or hyperplastic changes in arteriosclerosis. The author presents a 48-year-old white man with a negative history who died from a hepatoma of the liver. There were no clinical cardiovascular manifestations. At necropsy the heart weighed 265 grams and appeared entirely normal, except for a patch of atheroma in the left descending coronary artery. Histologically, the myocardium was normal. In the subepicardial tissue many small arteries and arterioles were found, rich in muscle fibers which showed deposits of amyloid localized to the media and occupying only parts of the circumference. In some vessels the lumen was almost obliterated. The color of this material was red-violet with hematoxyline-eosine. It gave the typical staining characteristics of amyloid. There were no changes in the endothelium and the adventitia and there were no inflammatory changes. In the area occupied by the amyloid, the nuclei, muscle fibers, and connective tissue were not recognizable. The author states that this lesion resembles hyaline arteriosclerosis. No trace of amyloid was found in the larger arteries, surrounding tissues, or in the rest of the body.

LENEL.

Cohn-Czempin, R.: Cinnabane in the Treatment of Angina Pectoris, Acta Med. Orient. 5:292 (Sept.), 1946.

The favorable effect of Cinnabane, a benzyl-cinnamide, on otosclerosis, as reported by Seelenfreund, suggested the use of this new drug for the treatment of angina pectoris. In view of the vasodilator effect of the benzyl radical and its lipoid-solubility, the drug was expected to have a lasting rather than a transient effect.

The results of treatment of seventeen cases of angina pectoris are reported by this author. A course of treatment consisted of ten daily intramuscular injections of a 1 c.c. solution in oil. This treatment could be repeated once or twice after an interval of one week.

In fifteen of the seventeen patients cinnabane proved to be a powerful and lasting vasodilator. Pain usually disappeared after the first course. In the presence of hypertension, the blood pressure dropped gradually and remained low for a long time.

In seven patients, improvement of electrocardiographic findings were recorded. The improvement consisted in the disappearance of S-T segment depression and return to normal of inverted T waves in Lead IV F.

The author concludes that cinnabane, owing to its lasting action as vasodilator, has proved of great value in the treatment of angina pectoris, as well as other forms of heart disease caused by coronary insufficiency.

Another advantage is that cinnabane therapy can be given periodically, while other vasodilators must be taken continually in order to suppress pain and anginal attacks.

BELLET.

Ben-Asher, S.: On the Toxicity of the Mercurial Diuretics: Observations on Eighteen Cases With Suggestions for the Prevention of Toxic Reaction. Ann. Int. Med. 25:711 (Oct.), 1946.

The author describes his experiences with 18 patients with congestive heart failure in whom the intravenous administration of a mercurial diuretic was followed by untoward symptoms, such as acute circulatory collapse or an acute cerebral episode manifested by delirium, drowsiness, or mental confusion. In 10 of the patients a delayed type of reaction occurred. Since nine of this number recovered after the administration of salt and water, the author ascribes the delayed reaction to excessive dehydration which resulted from the diuretic effect of the drug, superimposed on the excessive sweating which resulted from high environmental temperatures and humidity. An immediate untoward reaction occurred in eight other patients, but in seven of these, the repetition of such a reaction was prevented either by giving the drug slowly and intermittently or by preceding the injection with the intravenous administration of sodium thiosulphate. It is also the author's opinion that the occurrence of either type of reaction increased the seriousness of the prognosis; for this reason he strongly recommends a consideration of all factors which might prevent either form of reaction.

WENDKOS.

Lequine, J., Segers, M., and Denolin, II.: Tachycardia Produced by Venous Hypertension in Man. A Study of the Bainbridge Reflex. Acta Cardiologica 1:1, 1946.

The mechanism of the Bainbridge reflex was studied in man by the following procedures: (1) increasing the venous pressure in a series of eleven normal subjects by the injection of one liter of physiologic serum, warmed to 37° C., into an arm vein in a period of five to ten minutes; (2) altering the venous pressure in a patient who had an arteriovenous fistula of the femoral vessels by intermittent compression of the fistula. During both procedures, records were made of the venous and arterial pressures and of the heart and respiratory rates.

The intravenous injections were followed by an increase in venous pressure of 5 to 74 mm. of water. The heart rate was accelerated by 8 to 25 per cent. In four subjects, 1.5 to 2.0 mg. of atropine was administered and during the resultant acceleration of the heart, the infusion was repeated. It was found that although the venous pressure increased as before, there was no appreciable increase of the heart rate. An exercise test after atropinization, on the other hand,

increased the heart rate by about 20 per cent. The possibility that an aortic reflex or increased respiratory movements were responsible for the cardiac acceleration during the infusion was excluded by the fact that the blood pressure change was very slight and that no significant change in respiratory rate was noted.

In the case of the arteriovenous fistula, closure of the fistula produced an initial increase of 30 mm. in the arterial pressure, but the pressure fell promptly to its original level in spite of the fistula remaining closed. The venous pressure, on the other hand, decreased to 25 mm. of water below its initial level and this hypotension persisted. The heart rate decreased from 100 to 60 beats per minute and then maintained a constant rate of 75. The association of the slower heart rate and lower venous pressure in the presence of a relatively unchanged arterial pressure was considered further evidence of the existence of the Bainbridge reflex. The administration of 1.5 mg. of atropine completely suppressed the response of the heart to compression of the fistula.

Acceleration of the respiratory rate by over 10 per cent occurred during the infusion of serum in eight of the eleven cases. On the other hand, altering the venous pressure by compressing and opening the fistula did not change the respiratory rate. When the venous pressure was elevated by infusion in the four subjects who received atropine, there was no increase in the respiratory rate. This respiratory reaction as it occurs in man is considered comparable to that described in the dog but is inconstant.

The Bainbridge reflex is concluded to be an important but partial element in determining exercise tachycardia.

LAPLACE.

Goldfinger, D., and Wosika, P. H.: The Electrocardiographic Effects of Prostigmine.
Am.J.M.Sc. 212:418 (Oct.), 1946.

The fact that tachycardia remains a difficult problem therapeutically and often interferes with the proper evaluation of the myocardial status through the interpretation of the electrocardiogram led the authors to study the effects of prostigmine. The study was felt to be especially indicated because of recent reports extolling the effect of this medication in all forms of tachycardia. The electrocardiographic changes were therefore observed in forty-two patients to whom 1 mg. of prostigmine methylsulfate was administered subcutaneously. The cardiac rate was slowed in 86 per cent of the patients studied. The series included patients with both organic and functional conditions. While this slowing may have been as little as 10 beats per minute in some instances, yet a similar result could not be obtained by any other method. Besides a decreased rate, other effects were noted, including transient inversion of the P wave, increase in amplitude of the QRS, increase in the amplitude of the T waves, separation of the fused T and P wave in auriculoventricular block, and slowing of the ventricular rate in auricular fibrillation and auricular flutter. Most of the effects upon the form of the electrocardiogram were explained upon the basis that the rate is slowed by stimulation of the parasympathetics. The P-R interval was uninfluenced except in one case of neurocirculatory asthenia in which it was shortened from 0.18 to 0.16 second and in one case of rheumatic heart disease in which it was lengthened from 0.16 to 0.18 second. The effect of the oral preparation of prostigmine bromide was disappointing when used therapeutically, notable slowing being achieved only with doses which produced intolerable side effects.

The procedure recommended in the study of the electrocardiogram is the comparison of the complete electrocardiogram before and twenty minutes after the injection.

DURANT.

Breytspraak, R. W., and Greenspan, F. S.: The Effect of Aminophylline on the Prothrombin Time in Man. *Am.J.M.Sc.* 212:476 (Oct.), 1946.

Aminophylline was administered orally and intravenously, in full dosage, to a small series of young adult, male patients with mild bronchial asthma. The effects of the drug were studied with respect to the changes in the dilute (12.5 per cent) plasma prothrombin time. No significant

hyperprothrombinemia could be demonstrated in any of these cases. This is in contrast to previous observations, and would seem to indicate that fear of increased clotting tendencies suggested by these previous studies is unwarranted.

DURANT.

Priest, W. S., Smith, J. M., and McGee, C. J.: The Effect of Anticoagulants on the Penicillin Therapy and the Pathologic Lesion of Subacute Bacterial Endocarditis. New England J. Med. 235:699 (Nov. 14), 1946.

Thirty-four patients with subacute bacterial endocarditis were treated with penicillin. Twelve of these received either heparin or dicumarol or both from the outset of penicillin therapy, three received anticoagulants with the penicillin only in the last of several courses of therapy, and nineteen were treated without anticoagulants. Difficulty was experienced in maintaining the desired coagulation time when heparin was administered, and in maintaining the desired prothrombin time after dicumarol. Considerable variation in individual response was observed with both drugs. In three patients, embolic phenomena disappeared after anticoagulants were given, but in five, embolism first appeared during their administration, and two additional patients suffered massive, fatal hemorrhages while receiving anticoagulants. This complication was not observed in any of the nineteen control cases. Of the fifteen patients to whom anticoagulants were given, eight died; whereas of the nineteen treated with penicillin alone only five died. However, the doses of penicillin given were not uniform, and the incidence of recovery was related to the size of daily penicillin dosage regardless of whether or not anticoagulants were given. Histologically no conclusive evidence in favor of anticoagulants could be demonstrated. The amount of fresh fibrin present on the valvular lesions was not demonstrably less than in untreated patients.

The authors conclude that no evidence was found that anticoagulants are a necessary adjunct to penicillin therapy in the treatment of subacute bacterial endocarditis.

KAY.

Holman, E.: Roentgenologic Kymographic Studies of the Heart in the Presence of an Arteriovenous Fistula and Their Interpretation. Ann. Surg. 124:920 (Nov.), 1946.

Roentgenologic kymography provides important observations on the effect upon the heart and large vessels of closing a large arteriovenous fistula. The immediate effect is shown to be additional distention of an already dilated heart and aorta. This distention is due to backing up into the arterial bed of the blood formerly flowing through the fistula into the capacious venous bed. Since a large fistula of long duration is invariably accompanied by an increased total blood volume, the entire arterial bed, including the left heart and the aorta, is overdistended by this increased blood volume when the leak into the venous bed is suddenly closed. The immediate effect of such an overdistention of the arterial tree is a marked elevation of the systemic blood pressure, which is promptly though not completely rectified by a slowing of the cardiac contractions. This mechanism is dependent upon stimulation of the fibers of the depressor nerve in the arch of the aorta by the overdistention of this vessel which follows closure of the fistula and which is dependent upon the increase in total blood volume that occurs in the presence of a fistula of large size and long duration. The response is eliminated by atropinization of the patient and is therefore considered to be vagal in origin. If the fistula is closed permanently by operation, the blood pressure and heart rate return to normal through the gradual reduction of blood volume to normal. That the increase in blood volume and resulting circulatory effects occurs in all fistulas to greater or less degree seems likely, but these changes and effects are not always demonstrable by present instruments of precision or by present scientific methods in small fistulas with small increases in blood volume. In small fistulas also, these changes may be masked by other physiologic adjustments such as peripheral vasodilatation which may obviate the increase in general blood pressure when the blood volume increase is small.

NAIDE.

Shumacker, H. B., Jr., and Carter, K. L.: Tests for Collateral Circulation in the Extremities. Arch. Surg. 53:359 (Oct.), 1946.

The determination of the adequacy of collateral circulation prior to exploration for aneurysm or arteriovenous fistula is most important. The authors feel that the most reliable and practical preoperative test for collateral circulation is the reactive hyperemia test. Though of great practical help and general reliability, this test is not infallible. The chief difficulties arise from the occasional impossibility of accurate compression of the involved arteries at the exact site of the fistula or aneurysm without concomitant compression of neighboring uninvolved vessels. If an excellent and complete flush occurs promptly during the test, with no further improvement on release of the compressed artery, one may approach the aneurysm and ligate, if necessary, the involved artery with minimal risk of ischemic difficulty.

If one does not succeed in establishing collateral circulation which is adequate according to this test, exploration should be carried out with great caution. The hand or foot should be exposed during operation and should be observed for change in color and temperature during prolonged temporary occlusion of the involved segment of artery. If ischemia of the hand or foot prevails, extirpation of the lesion should be deferred unless it is perfectly evident that a cure can be effected with maintenance of continuity of the involved artery. All preoperative study of collateral circulation is based on the premise that no collateral vessels will be needlessly destroyed during operation and that no postoperative thrombosis will occur.

NAIDE.

Grand, M. J. H., Stanbury, J. B., Ekermeyer, E. W., and Purvis, J. D., Jr.: Rheumatic Fever: A Statistical Analysis of Incidence During Sulfadiazine Prophylaxis. U. S. Nav. M. Bull. 46:1793 (Dec.), 1946.

From December, 1943, to May, 1944, sulfadiazine was given to large groups of trainees at a naval training center as a prophylactic measure against streptococcal and other respiratory diseases. Specifically this drug was given to one regimental group, the complement of which ranged between four and five thousand men. Another regiment, whose complement ranged between two thousand five hundred and three thousand, received none of the drug and served as a control. There were eighteen cases of rheumatic fever in the treated group and twenty-six in the untreated group. Fifteen men developed rheumatic fever while still taking the drug; the other eleven became ill within four weeks after discontinuing prophylaxis. These figures are interpreted to indicate that in the group receiving sulfadiazine rheumatic fever was not eliminated but the number of cases was diminished.

BELLET.

Blalock, A.: The Surgical Treatment of Congenital Pulmonic Stenosis. Ann. Surg. 124:879 (Nov.), 1946.

The results of the surgical treatment of congenital pulmonic stenosis in 110 patients are reported. The main indication for operation is evidence of an inadequate flow of blood to the lungs. Important in the diagnosis is the absence of visible pulsations in the lung fields as observed under the fluoroscope, and roentgenographic evidence that the pulmonary artery is small in size. The typical case of the "tetralogy of Fallot" should not present great difficulties in diagnosis. There are, however, many borderline cases in which it is difficult or impossible to be certain of the true nature of the condition. If, under such circumstances, the patient has a hopeless prognosis without an operation, an exploration is indicated.

The technique of the operation is described. The various arteries used for anastomosis to a pulmonary artery are the subclavian, innominate, and the common carotid. Of the 110 patients operated upon, twenty-five have died, with an over-all mortality rate of 23 per cent. An anastomosis was performed between the end of a systemic vessel and the side of one of the two pulmonary arteries in ninety-one of the one hundred ten patients. There were sixteen deaths in this group. The subclavian artery was used in forty-six patients with four deaths. One of these was due to hemoptysis on the fifth day which was believed to have been caused by the use of

dicumarol. The innominate artery was used in thirty-six patients; there were eleven deaths in this group. The commonest cause of death in this group was cerebral anemia or thrombosis. The end of the carotid was anastomosed to the side of one of the pulmonary arteries in nine patients. There was one death in this group which occurred nine months after operation. An end-to-end anastomosis was attempted between the end of a systemic artery and the end of one of the two pulmonary arteries in ten patients. This method was used because the pulmonary artery was very short or small, or because the patient was extremely ill and haste was necessary. There were four deaths in this series. Anastomosis was not performed in six patients. In four of these the pulmonary arterial pressure was high and it was thought that anastomosis was not indicated. These patients survived the exploratory operation. The remaining two patients died.

Severe bleeding from the anastomosis did not occur postoperatively in any case. There was no significant interference with the circulation of the arm on the side on which the subclavian artery was sacrificed or used for the anastomosis in any of the patients. Weakness or paralysis of the opposite side of the body in patients in whom the innominate or carotid artery was used either had cleared up or was diminished in all who survived the operation. Although some of the operations were performed too recently to allow an evaluation, it appears that all of the patients, with one exception, who have survived the performance of an anastomosis are improved. Heart failure or *Streptococcus viridans* endarteritis has not developed thus far in any of the patients.

NAIDE.

Master, A. M.: Effect of Injury and Effort on the Normal and the Diseased Heart.
New York State J. Med. 46:2634 (Dec.), 1946.

This author discussed the relation of injury and effort to the onset of heart disease and to the production of exacerbations of symptoms in the presence of pre-existing heart damage. This subject is discussed particularly from the point of view of workmen's compensation.

The author believes that heart failure does not follow overexertion when the heart is normal. Effort probably never produces valvular damage if the valve is previously normal, although trauma in rare instances may cause rupture of a normal valve. A forceful impact of the chest wall against the heart results in damage to the heart muscle, usually in the form of hemorrhage; if the impact is severe, the heart and blood vessels may be ruptured. Trauma which is not so severe as to produce morphologic changes in the heart may produce disturbances in the heart function manifested chiefly by irregularities in rhythm. Contusion of the heart does not usually precipitate the classic type of coronary occlusion or thrombosis. Master is of the opinion that attacks of acute coronary occlusion are apparently unrelated to either exertion or occupation. Whether a causal relationship exists between effort and local hemorrhage or thrombosis in the brain has not been satisfactorily determined.

The presence of hypertension in association with dissecting aneurysm has led some authors to maintain that the dissection may be initiated by some unusual exertion or that effort causes rupture and fatal hemorrhage. No evidence was found to support the theory that elevated blood pressure is essential for the initiation of the dissecting aneurysm.

It is doubtful whether exertion or injury ever precipitates acute rheumatic fever. Trauma with resulting secondary infection may produce malignant endocarditis but not subacute bacterial endocarditis.

The author believes that severe trauma may produce rupture of an aortic aneurysm, but effort does not. When patients with narrowing of the coronary ostia due to syphilitic aortitis are subjected to effort, excitement, or similar stress, acute myomalacia without acute coronary occlusion may result.

A person with neurocirculatory asthenia cannot perform heavy physical work; his symptoms may be aggravated temporarily by accidents or effort. Arrhythmias may result from heavy work or unusual physical strain or following an accident.

Heart failure will not be observed in a normal man or woman as a result of unusual effort or trauma, but a diseased heart may fail under the stress of unusual effort or as a result of trauma.

BELLET.

Freeman, N.: Arterial Repair in the Treatment of Aneurysms and Arteriovenous Fistulae. *Ann. Surg.* 124:888 (Nov.), 1946.

The incidence of gangrene due to acute ischemia following operations on aneurysms and arteriovenous fistulas is rare. Not a single instance occurred in 100 patients operated upon at the DeWitt General Hospital. There was but one case in the entire series of patients in the three Vascular Centers of the U. S. Army. This splendid record is probably due both to the policy of waiting a sufficient length of time for the development of collateral circulation and to the perfection of surgical technique designed to spare the important collaterals. In addition, prophylactic sympathectomy may have helped in practically abolishing gangrene after operations on arterial lesions.

Although there is sufficient circulation to care for the metabolic needs of the tissues at rest, interruption of the major artery to a limb may lead to persistent symptoms of impaired circulation such as intermittent claudication. Arterial repair was attempted in the treatment of twenty-three aneurysms and arteriovenous fistulae. Success was demonstrable either by arteriography or by the presence of normal peripheral arterial pulsations in eighteen of these attempts. In one case, recurrence of an arterial aneurysm was subsequently reported by the patient. In a second patient, recurrence of an arteriovenous fistula followed transvenous suture and subsequent excision of the lesion was necessary. Thrombosis at the suture line occurred in three of the twenty-three patients but the collateral circulation proved sufficient to prevent gangrene.

Repair of the defect in the wall of the vein was performed on 18 patients. After the recovery of 12 of these patients, phlebography demonstrated the patency of the vein in six patients, but in six others postoperative studies showed the vein to be occluded. No instance of thrombophlebitis or pulmonary embolism was encountered.

Transverse suture of the defect in the arterial wall after excision of the damaged portion has been found more satisfactory than longitudinal suture, end-to-end anastomosis, or transvenous repair. Oscillometry has demonstrated marked improvement in the circulation in patients after repair of arterial lesions. The functional capacity, especially as shown by freedom from intermittent claudication, is increased in patients when the continuity of the major artery to the extremity is preserved.

NAIDE.

Winton, S. S., and Wallace, L.: An Electrocardiographic Study of Psychoneurotic Patients. *Psychosom. Med.* 8:332 (Sept.-Oct.), 1946.

The authors analyzed the electrocardiographic records of seventy-six psychotic and neurotic patients, shown by physical examination and functional inquiry to be free of organic heart disease, in order to determine whether certain combinations of electrocardiographic changes could be found which formed any definite pattern characteristic of this type of patient.

Twelve per cent of these patients showed right ventricular hypertrophy; as seen by tall P waves, right axis deviation and RS-T segment depression in the limb leads. Deep S waves as an isolated abnormality occurred almost as frequently as in routine electrocardiograms of normal young individuals.

Flat or inverted T waves in Leads I and II occurred about fifteen times as frequently in psychoneurotic patients as in a large group of young healthy aviators. RS-T depressions of at least 0.5 mm. in Leads I and II were about six times as frequent as in normal individuals.

It was concluded that there is no combination of abnormalities which fits a distinct electrocardiographic pattern characteristic of this group of patients.

BELLET.

Wolf, G. A., and Wolff, H. G.: Studies on the Nature of Certain Symptoms Associated With Cardiovascular Disorders. *Psychosom. Med.* 8:293 (Sept.-Oct.), 1946.

These authors focused their study upon the reactions of a small group of individuals to a variety of life situations, with special reference to the effect of these situations upon cardiovascular and respiratory functions. Emphasis was placed upon the reactions to persistent low-grade stresses and strains which are a part of everyday living rather than upon the well-known responses

to the major crises of life. Attempts were made to ascertain to what extent efficiency of the cardiovascular and respiratory systems was impaired during certain life situations, what the identifiable emotional responses were, and how these various reactions bear upon symptoms and disease.

Statements in the literature concerning the effect of anxiety upon bodily functions are common. Unfortunately, such references focus attention upon the emotional aspects of the response to a situation rather than upon the effect of the situation upon the entire organism. It is the latter conflict which is important to the physician.

These studies revealed the following: dyspnea and palpitation, associated with inefficient pulmonary ventilation, may occur in response to stress-producing life situations which are associated with anxiety, anger, guilt, rage, frustration, and tension. Heart pain, in the presence of anatomical narrowing of the arteries, may result from a fall in the cardiac output and coronary blood flow in association with desperation and defeat. Stress-producing situations increase the work of the heart as shown by increases in blood pressure and cardiac output. The normal heart under strain is able usually to withstand this increased work without manifesting pain.

Giddiness and faintness may result from cerebral anoxia attendant upon diminished venous return to the heart. Giddiness and faintness may also result from hyperventilation which is followed by cerebral vasoconstriction, impaired dissociation of oxyhemoglobin, and cerebral anoxia. Cerebral anoxia may occur in response to stress-producing life situations in association with feelings of exhaustion, anxiety, fear, and during the early part of convalescence. Fatigue is a complex state which may be dependent upon emotional attitude, the absence of a dominant motivation, and the presence of a stress-producing life situation with accompanying inefficiency of cardiovascular and respiratory function. Individuals differ considerably as regards the intensity and duration of the cardiovascular and respiratory responses to life situations.

These results indicate that, in a setting of adverse life circumstances and associated emotional reactions, performance is costly, in terms of respiration and work of the heart. This high cost may manifest itself in cardiovascular symptoms which are not dependent alone upon gross structural disorder.

BELLET.

Schroeder, E. F., Rose, F. A., and Most, H.: *Effect of Antimony on the Electrocardiogram*. *Ann. J. M. Sc.* 212:697 (Dec.), 1946.

Trivalent and pentavalent antimony compounds have been used extensively in the treatment of human schistosomiasis and leishmaniasis and more recently to a limited degree in human filariasis. The major application of antimony as a therapeutic agent in the recent war has been its use in the treatment of *Schistosomiasis japonica*. Fuadin and tartar emetic are the drugs principally used in the treatment of this infection. Attempts have been made to explain sudden deaths which occasionally occur during such therapy on the basis of myocardial changes. The authors therefore have analyzed 315 electrocardiograms made on 100 patients during various stages of treatment with tartar emetic and fuadin for schistosomiasis infection. The changes noted included an increased amplitude of P waves in Leads II and III (found in 11 per cent of the patients), a fusion of the ST segment and T waves (found in 45 per cent), varying degrees of decrease in amplitude of the T waves (found in 99 per cent), and abnormal prolongation of the Q-T interval (found in 27 per cent). Deep inversion of the T waves occurred in many of the cases. The duration of these changes was variable; the changes were present up to two months after cessation of treatment. The etiology and significance of the changes remain unknown. It is the authors' opinion that these changes represent a transient side action of antimony and are not indicative of cardiac damage or serious impairment of cardiac function. They emphasize the fact that recent antimony therapy must be considered in evaluating abnormal electrocardiograms found in veterans and others.

DURANT.

McPeak, E. M., and Levine, S. A.: The Preponderance of Right Hydrothorax in Congestive Heart Failure. *Ann. Int. Med.* 25:916 (Dec.), 1946.

The authors speculate upon the various mechanisms which might operate in congestive heart failure to localize pleural effusions in the right chest. Although no final conclusions are made, they suggest that exudation from visceral pleural capillaries secondary to anoxia in combination with impaired lymphatic drainage may be important contributory factors. The opinions expressed are based on an analysis of seventy-five cases requiring thoracentesis, fifty-two cases in whom effusion into the pleural cavity had been demonstrated by the roentgenologist but in whom thoracentesis had not been done, and an additional 110 cases in whom effusion into the pleural sac had been found at autopsy. In the first group, the effusion was limited to the right side in 75 per cent of the cases with rheumatic heart disease, and in 50 per cent of the cases with hypertensive and arteriosclerotic heart disease. In the second group, it occurred in one-half of the cases of rheumatic heart disease and in one-third of the cases of hypertensive and arteriosclerotic heart disease. In the third group, the effusion was only rarely limited to a single pleural cavity. Of those who at necropsy showed bilateral effusions, larger amounts were estimated to be present in the right chest in forty-four out of fifty-five cases of rheumatic heart disease and in thirty-six out of forty-eight cases of hypertensive and arteriosclerotic heart disease.

WENDKOS.

Russek, H. I., Cutler, J. C., Fromer, S. A., and Zohman, B. L.: Treatment of Cardiovascular Syphilis With Penicillin. *Ann. Int. Med.* 25:957 (Dec.), 1946.

Fifteen consecutive cases of cardiovascular syphilis, including four with aortic aneurysm, were treated with penicillin in the dosage of 40,000 units every two hours for 85 doses. No significant untoward reactions which necessitated discontinuance of the drug were encountered. Four cases showed distinct improvement in coronary reserve following treatment. Electrocardiographic confirmation of such improvement was not obtained. In one instance, mild substernal pain recurred intermittently at rest on the third day of treatment, but disappeared after several hours without interruption of therapy. It is concluded that harmful reactions to penicillin are uncommon in cardiovascular syphilis during the treatment and early post-treatment periods, and that this form of therapy warrants further evaluation.

WENDKOS.

Gordon, L. Z., and Thurber, D. C.: Temporal Arteritis: Report of a Case and a Comparison With Respect to Periarteritis Nodosa. *Arch. Path.* 42:402 (Oct.), 1946.

The authors report a case of arteritis of the temporal artery occurring in a 65-year-old man who complained of severe headache, pain over both temporal regions, and severe pain in both thighs. These symptoms were accompanied by fatigue, anorexia, fever, anemia, and rapid sedimentation rate. Biopsy of the tender pulsating temporal arteries revealed active arteritis with epithelioid, lymphocytic, and granulomatous cellular infiltration throughout all the arterial coats. Multinucleated giant cells were present. The clinical findings indicated an infectious basis for the temporal arteritis; bacteriologic and serologic studies failed to reveal a bacteriologic factor.

The authors feel that the pain in the thighs was a part of the clinical picture, and that the disease known as temporal arteritis is in reality only a part of a widespread polyarteritis. They based their conclusion on a comparison of the findings in their case with reports of necropsy examinations in this disease, in which it was pointed out that many arteries exhibit the same pathologic changes as do the temporal vessels.

The writers find it difficult to differentiate this disease from periarteritis nodosa on the basis of cellular reaction. They believe that the histologic pictures are similar in both diseases. They point out, however, that periarteritis nodosa generally involves visceral arteries and less commonly the peripheral arteries; whereas temporal arteritis, only occasionally found in visceral arteries, is commonly present in the aorta, the innominate, carotid, subclavian, and iliac arteries as well as the temporal vessels. They also emphasize the fact that periarteritis nodosa is a fatal disease while in temporal arteritis the prognosis is generally good.

GAULEY.

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THE American Heart Association was founded in 1924 "for the study of and the dissemination and application of knowledge concerning the causes, treatment and prevention of heart disease; the gathering of information on heart disease; the development and application of measures that would prevent heart disease; seeking and provision of occupations suitable for heart disease patients; the promotion of the establishment of special dispensary classes for heart disease patients; the extension of opportunities for adequate care of cardiac convalescents; the promotion of permanent institutional care for such cardiac patients as are hopelessly incapacitated from self-support; and the encouragement and establishment of local associations with similar objects throughout the United States."

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The American Council on Rheumatic Fever, organized in 1944, consists of a group of representatives of all national medical organizations concerned with rheumatic fever. It operates administratively through the American Heart Association and carries out the program of the American Heart Association insofar as that relates to rheumatic fever.

Annual membership in the American Heart Association is \$2.50 and includes twelve issues of *Modern Concepts of Cardiovascular Disease*; Journal membership is \$10.00 and includes a year's subscription to the *AMERICAN HEART JOURNAL* (January-December), twelve issues of *Modern Concepts of Cardiovascular Disease*, and annual membership in the Association. Contributing membership starts at \$25.00 per year; patron membership is \$50.00 and over per year. Membership blanks will be sent upon request.

The Association earnestly solicits your support and suggestions for its work. Donations will be gratefully received and promptly acknowledged.

Annual Meeting

The Annual Meeting and Twentieth Scientific Sessions of the American Heart Association will be held in Atlantic City, N. J., June 6 and 7, 1947. The Hotel President will be the headquarters for all meetings. On June 6, a meeting will be held with representatives of local Heart Associations to discuss the administrative structure of the American Heart Association with particular reference to program. The annual meeting of members will also be held on that day. The scientific sessions will take place on June 6 and 7. The annual dinner is scheduled for Saturday evening, June 7, at the Hotel President. Meetings begin at 9:00 A.M. each day, and members should plan to arrive on June 5. Hotel rooms will be in great demand and every member who wishes to attend is urged to make reservations immediately.

The chairman of the Program Committee for the Annual Scientific Sessions of the American Heart Association is Dr. Edgar V. Allen, Mayo Clinic, Rochester, Minn. All who desire to present papers at the meetings of June 6 and 7 in Atlantic City should forward to him an abstract of the proposed presentation of not more than 300 words. The deadline for the receipt of abstracts is March 30, 1947.

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Inter-American Number

As a recognition of its importance and as a contribution to its full success, the American Heart Association and the Editorial Board and publishers of its official JOURNAL are devoting this entire issue of the AMERICAN HEART JOURNAL to the transactions of the Second Inter-American Congress of Cardiology, which was held in Mexico City in October, 1946.

This issue has been made a large one in order that as many papers as possible might be published in full. Some contributions have appeared in earlier issues and some additional ones will appear in subsequent issues. The Board regrets exceedingly that it cannot publish every paper in full and that so many excellent papers must appear in an abbreviated form.

THE SECOND INTER-AMERICAN CONGRESS OF CARDIOLOGY AND THE FORMATION OF THE INTER-AMERICAN SOCIETY OF CARDIOLOGY

The second Inter-American Congress of Cardiology convened in Mexico City on Oct. 6, 1946, under the direction of its President, Professor Ignacio Chávez. The scientific sessions were held at the National Institute of Cardiology of Mexico, of which Dr. Chávez is the Director.

The sponsoring societies and institutions were as follows:

Sociedad Interamericana de Cardiología
The American Heart Association
Sociedad Argentina de Cardiología
Sociedade Brasileira de Cardiologia
Sociedad Cubana de Cardiología
Instituto Nacional de Cardiología de México
Secretaría de Salubridad y Asistencia Pública de México
Secretaría de Relaciones Exteriores de México
Universidad Nacional Autónoma de México

The Board of Directors and Honorary Members included leading officials of the Republic of Mexico headed by President Avila Camacho.

Honorary guests of the Congress were the following:

- Dr. Joseph Brumlik, Profesor de la Universidad de Praga (Czechoslovakia)
- Dr. Pierre Duchosal, Médico Adjunto del Hospital Universitario de Ginebra (Switzerland)
- Dr. Gaston Giraud, Decano de la Facultad de Medicina de Montpellier (France)
- Dr. Charles Laubry, Presidente de la Sociedad Francesa de Cardiología, Miembro de la Academia (France)
- Dr. Jean Lequime, Delegado de la Sociedad Belga de Cardiología (Belgium)
- Dr. Ivan Mahaim, Profesor de la Universidad de Lausanne (Switzerland)
- Dr. Gustav Nylin, Profesor de Clínica Médica en el Sabbatsbergs Sjukhus de Estocolmo (Sweden)
- Dr. V. Puddu, Director del Centro para la Lucha contra el Reumatismo y las Cardiopatías, del Policlínico de Roma (Italy)
- Dr. Daniel Routier, Delegado de la Sociedad Francesa de Cardiología (France)
- Dr. J. Snellen, Delegado de la Sociedad Holandesa de Cardiología (Holland)
- Dr. Eric Warburg, Profesor de Medicina Interna en el Rigshospitalet de Copenhague (Denmark)

The session opened at the Bolívar Amphitheatre of the University on Sunday, October 6, and the scientific meetings continued daily through the week at the National Institute of Cardiology where the members had an opportunity to see a building and equipment dedicated to the study of cardiovascular disease which are unique in the history of cardiology.

On hundred eleven papers were on the program for the four and one-half days. They were delivered in Spanish, English, French, and Portuguese. Abstracts in English or Spanish were available at each meeting for members unable to understand the language of the one delivering the address, and in the larger meetings Spanish- and English-speaking members were available to translate the discussions orally for the audience.

The social diversions to which the members were invited were splendidly organized and lavish. These included a luncheon at Montezuma's ancient palace of Chapultepec, a banquet with a demonstration of Mexican folklore and art, a luncheon and visit to the pyramids of San Juan Teotihuacán, and a reception and ball at the palace of the Secretary of Foreign Relations.

On October 11 a business meeting was held at which a permanent Inter-American Society of Cardiology was formed and a constitution adopted. Dr. Ignacio Chávez was elected Honorary President for life and the National Institute of Cardiology of Mexico designated the permanent secretariat. This Society is to be under a Council of Directors of which five represent South and Central America and five North America. The Directors from the South are

Dr. Ramón Aixalá (Cuba), Dr. Herman Alessandri (Chile), Dr. Eduardo Braun Menéndez (Argentina), Dr. Teófilo Ortiz Ramírez (Mexico), and Dr. Jairo Ramos (Brazil). Those from the North are Dr. Arlie Barnes (Rochester, Minn.), Dr. George R. Herrmann (Galveston, Texas), Dr. William Kerr (San Francisco, Calif.), Dr. Howard B. Sprague (Boston, Mass.), and Dr. John Hepburn (Toronto, Ontario, Can.).

The constitution was signed by Dr. Teófilo Ortiz Ramírez, Dr. Rodolfo Pérez de los Reyes, Dr. Howard F. West, Dr. Francisco Laranja, Dr. Luis V. Decourt, and Dr. Alberto C. Taquini for the Cardiac Societies of the countries of Mexico, Cuba, United States, Brazil, and Argentina.

The Society plans to meet every two years, the next time in 1948 in the United States. At the time of organization of the Society an International Council was also appointed to arrange an international Congress every six years.

The formation of this Inter-American Society of Cardiology and of the International Council is an important step in the history of the cooperative study of cardiovascular disease. Science is without boundaries, but individuals are nationalistic. The members of the Second International Congress know from their delightful and stimulating experience in Mexico that this interchange of social and medical ideas will be of benefit to both sides of the Rio Grande.

DIRECT INTRACARDIAC ANGIOCARDIOGRAPHY— ITS DIAGNOSTIC VALUE

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USING the Forssmann^{1,2} technique of heart catheterization, Egaz Monis, Lopo Carvalho, and Alen Saldana⁵ injected concentrated solution of iodide through the catheter and with x-ray exposures at the end of the injection obtained beautiful images of the great vessels. They called their method *pneumoangiography* and in 1931, applied this method to the study of the great vessels in tuberculous patients.

In 1937 Castellanos and co-workers⁶⁻⁸ published a method by which visualization of the heart chambers could be obtained in living persons. The method consists of rapid injection of radiopaque substance (35 or 50 per cent Per-Abrodil or uroselectan) into the venous blood stream through the antecubital veins, the amount injected varying from 10 to 15 c.c. according to the child's age. Films should be overexposed. This method, angiocardiology, is very useful and has made possible the diagnosis of many congenital heart anomalies.

A year later, in 1938, Robb and Steinberg⁹ applied the method to adults. It was necessary to modify the amount and the concentration of the dye, the average amount used being 30 to 40 c.c. of a 70 per cent solution. In addition, by determining the circulatory time (T.C.S.) and filming the right and left chambers at the proper moments, they obtained for the first time the image of the left chambers and the aorta. Unfortunately, the high opacity obtained by Castellanos in children could not be attained in adults. Nevertheless, in some fortunate cases, Robb, Steinberg, Sussman, Taylor, and McGovern and associates^{9,11-15} have been able to obtain good diagnostic films of the left atrium in mitral rheumatic heart disease and of the aorta and aortic aneurisms.‡

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‡After the reading of this paper we received a communication from Dr. Pérez Ara³ of Cuba and the reprint of his paper, "Right Heart Catheterisation," published in July, 1931, in *Revista de medicina y cirugía de la Habana*. Dr. Pérez Ara claims priority for the introduction of the catheter into the right heart through the internal jugular veins. He passed a Nelaton catheter up to the right auricle, and, after injecting 20 c.c. of a 50 per cent solution of sodium iodide he made an exposure at the end of the injection. By this method he obtained very clear visualization of the lung vessels. Dr. Pérez Ara in this experiment, as did Egaz Monis in his *pneumoangiography*, used a normal thoracic x-ray technique. If they had used a more penetrating exposure, they would certainly have obtained the visualization of the heart chambers. This was the fundamental change in technique made by Castellanos and associates.⁴⁻⁸

In 1946 one of us, (A. Celis) who is mainly interested in lung and mediastinal problems, modified the method with good results and applied the modified technique to heart problems.

TECHNIQUE

The reasons why Castellanos' method does not give clear-cut results are the following: (1) the relatively long distance that the opaque substance must travel from the antecubital veins to the heart; (2) too much dilution of the opaque substance with nonopaque blood; and (3) a shunt of the opaque material to undesirable veins.

To avoid these defects it is necessary (1) to put the opaque substance in the place where it is needed, if possible; (2) to fill the part to be visualized completely; and (3) to inject the substance very rapidly to avoid too much dilution.

In addition to these conditions, the opaque substance must be very opaque to x-rays, nonirritating to the endothelium, nontoxic, and easily and rapidly eliminated.

The new method consists of the introduction of a rubber catheter directly into the right atrium, or right ventricle if desired, through the external jugular vein which has been exposed. Fluoroscopic control of the position of the catheter, determination of T.C.S. through the catheter, and a very rapid injection of radiopaque substance are necessary parts of the technique. We commonly use 50 c.c. of 70 per cent solution of diodrast, but we have used as much as 90 c.c. in very large hearts. The injection time should be 0.75 second to 1 second. We take films routinely during or at the end of the injection; others are made according to T.C.S. at intervals of one, two, and three or more seconds. The full technical details are contained in Celis' paper which is in press.

The dissection of the jugular vein and the introduction of the catheter through this vessel might seem dangerous. The procedures are really only impressive; they are not more dangerous than the introduction of a catheter through any other vein. The advantage of the jugular over the antecubital route is that the former permits the introduction of a sufficiently large catheter (number 12 or number 14) to make possible the rapid injection of enough material to produce correct opacification of the heart chambers.

It is interesting to note that in pyelography there have been fatalities. In spite of the fact that highly concentrated dyes are rapidly introduced while performing angiocardiology, no fatalities are known to have followed this procedure.*

NORMAL IMAGE

The excellent results obtained by these methods are similar to those obtained in post-mortem studies by Chapuon, Laubry, Cottenot, Routier, and Heim de Balsac in adults and by Castellanos in infants.

*After this paper was written, there was a fatal accident at the General Hospital. The patient had advanced rheumatic heart disease, with double mitral lesion and auricular fibrillation. Six hours after angiocardiology was performed, the patient had symptoms of pulmonary embolism and died three days later. Post-mortem examination could not be made, so we do not know what role the angiocardiology may have played.

A careful review and comparison of their results with ours and with those obtained by American authors has enabled us to confirm some known facts and to discover others. The latter will be only briefly referred to in this paper since they will be the subject of more extensive research.

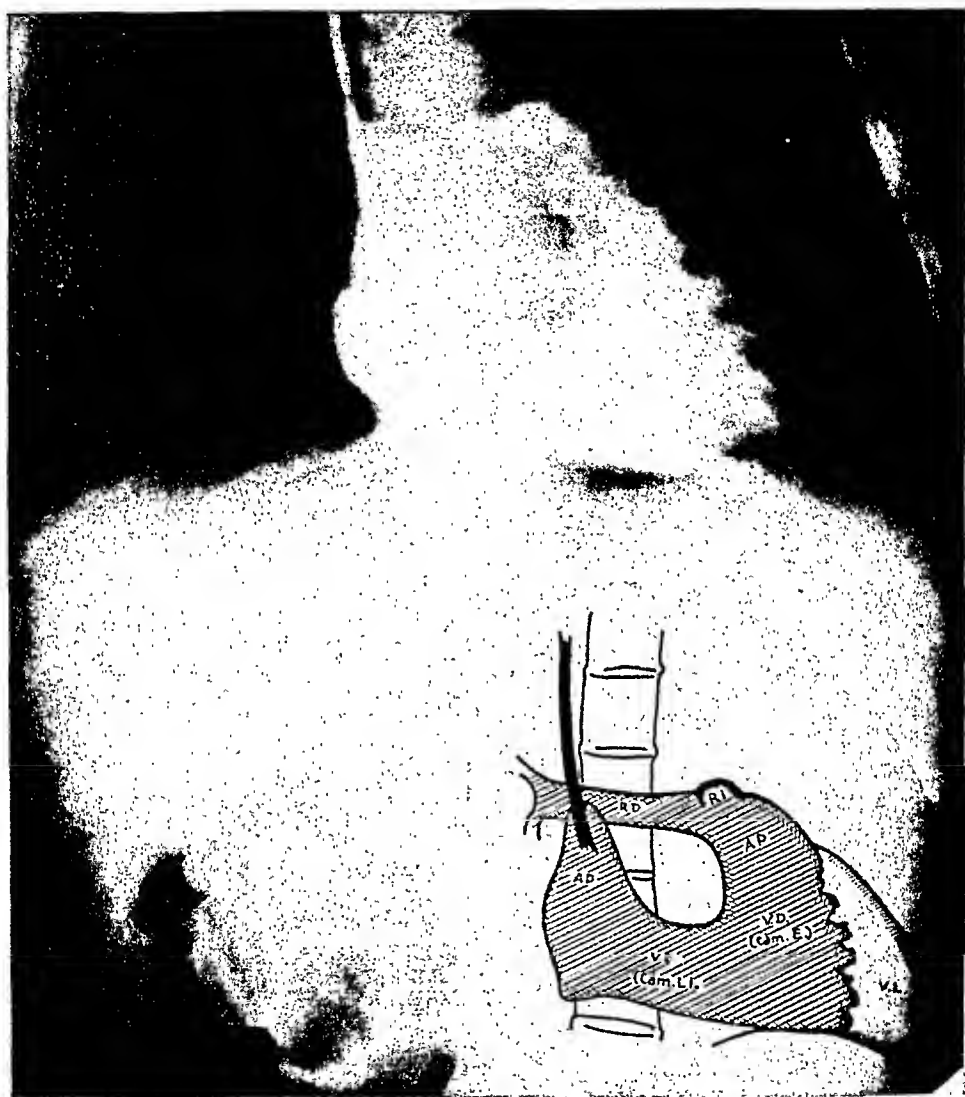


Fig. 1.—Angiocardiogram of right chambers of normal heart.

It is already well established that the right chambers are U shaped (Fig. 1). The superior vena cava and right atrium constitute the right limb of the U. Its projection is a little to the right of the vertebral column, and does not reach the diaphragm. The inflow tract of the right ventricle forms the horizontal limb. The outflow tract of the right ventricle forms the lower two-thirds of the left limb of the U; while the pulmonary artery forms the upper third of this limb. Between the right and horizontal limb, and between the lower two-thirds and

the upper third of the ascending limb there are often seen notches which we think are due to the tricuspid ring and to the pulmonary sigmoid valves respectively. We wish to point out (Fig. 2) that the pulmonary artery itself is not so near the

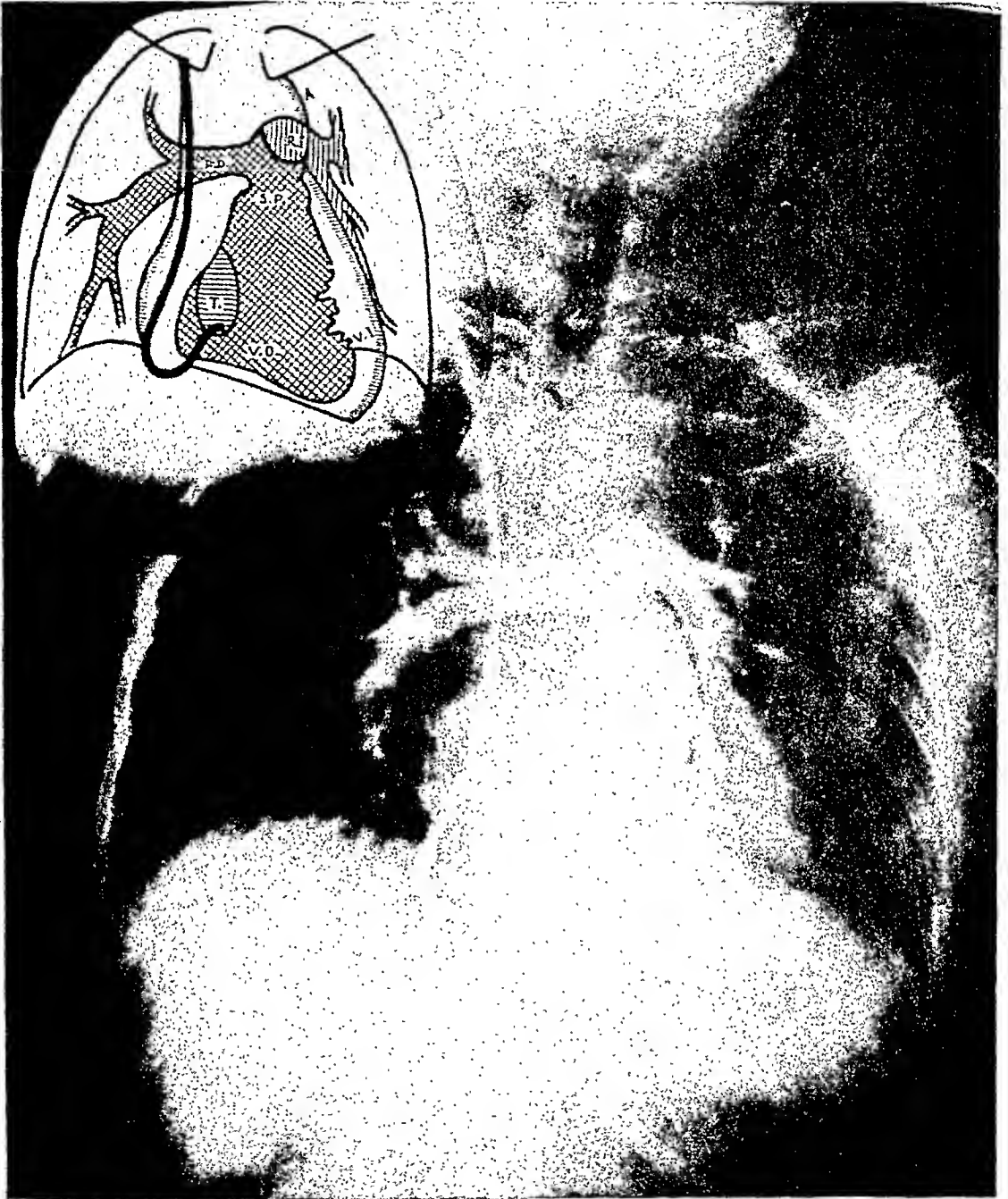


Fig. 2.—Angiocardiogram of normal heart. The pulmonary artery and branches are opaque. Relation of pulmonary artery to left border of cardiac silhouette is well shown (see text).

left border as has been thought. It is only the very highest part of the left middle arc of the cardiac silhouette that is formed by the pulmonary artery proper. The left branch comes off at a right angle to the main artery. The direction

of the left branch is at first backward but the course soon becomes a downward one. It is this descending branch and not the main pulmonary artery that forms the greater part of the middle arc of the left side of the cardiac silhouette. In other words, the left middle arc is formed in a very small part by the pulmonary



Fig. 3.—Same case as shown in Fig. 2. Pulmonary arteries and right branches are particularly shown.

artery itself; the rest is formed by the left descending branch. We have never seen the pulmonary conus placed so far to the left as to form a projection on the middle arc of the left border of the heart.

The right branch also comes off at a right angle, but its course is toward the right side of the chest. At approximately the right border of the vertebral column, it usually divides into two branches, less frequently into three. These branches spread outward rapidly. The right descendant branch is the largest. These branches are the most important shadows of the right hilum (Figs. 3, 4, and 5).

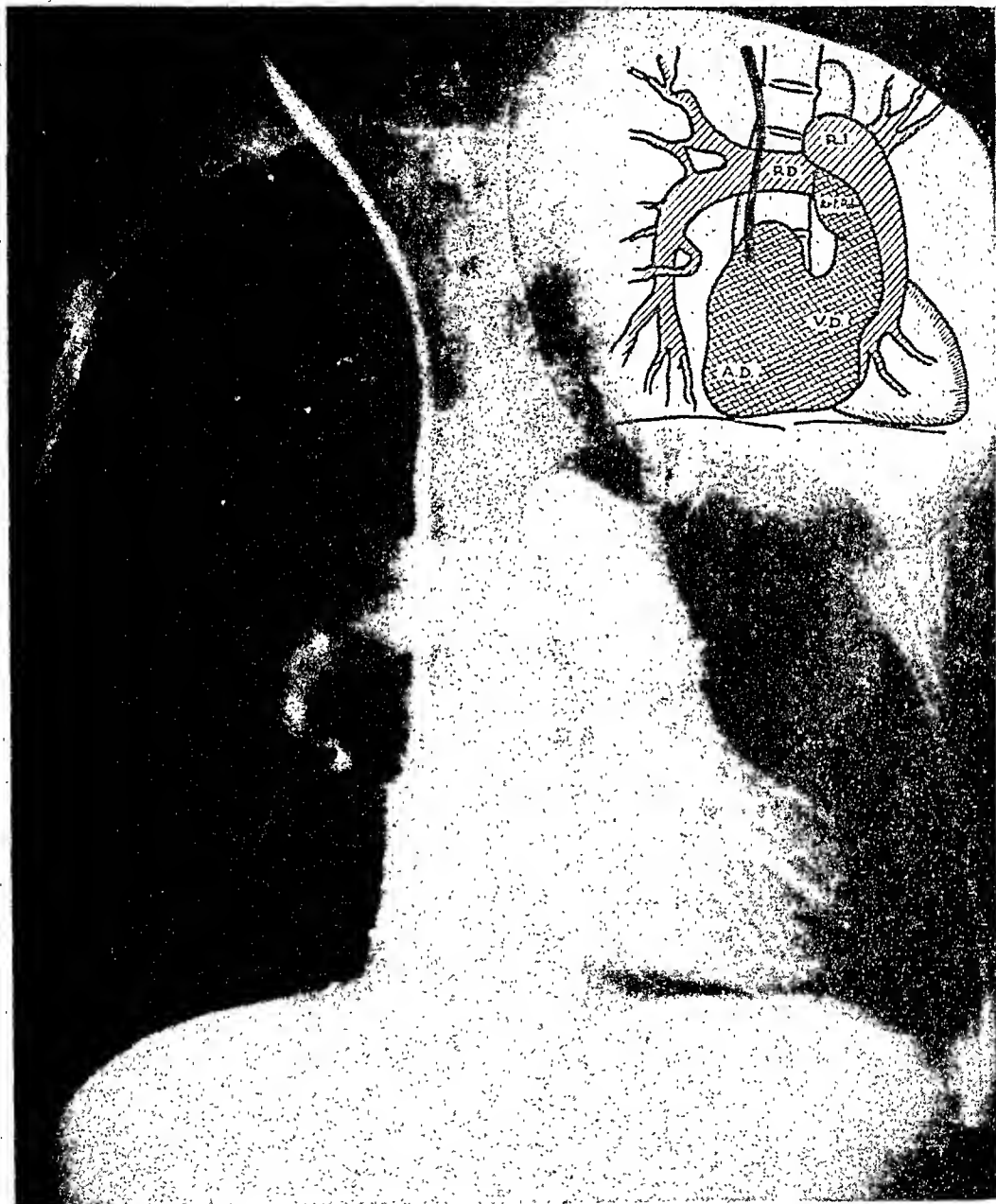


Fig. 4.—Same case as shown in Figs. 2 and 3. Pulmonary arteries and right branches are particularly shown.

We shall now describe the picture of the right heart in the lateral position (Fig. 6). In this position the superior vena cava is usually situated in the middle third of the chest. As it descends in a very gentle curve, it becomes

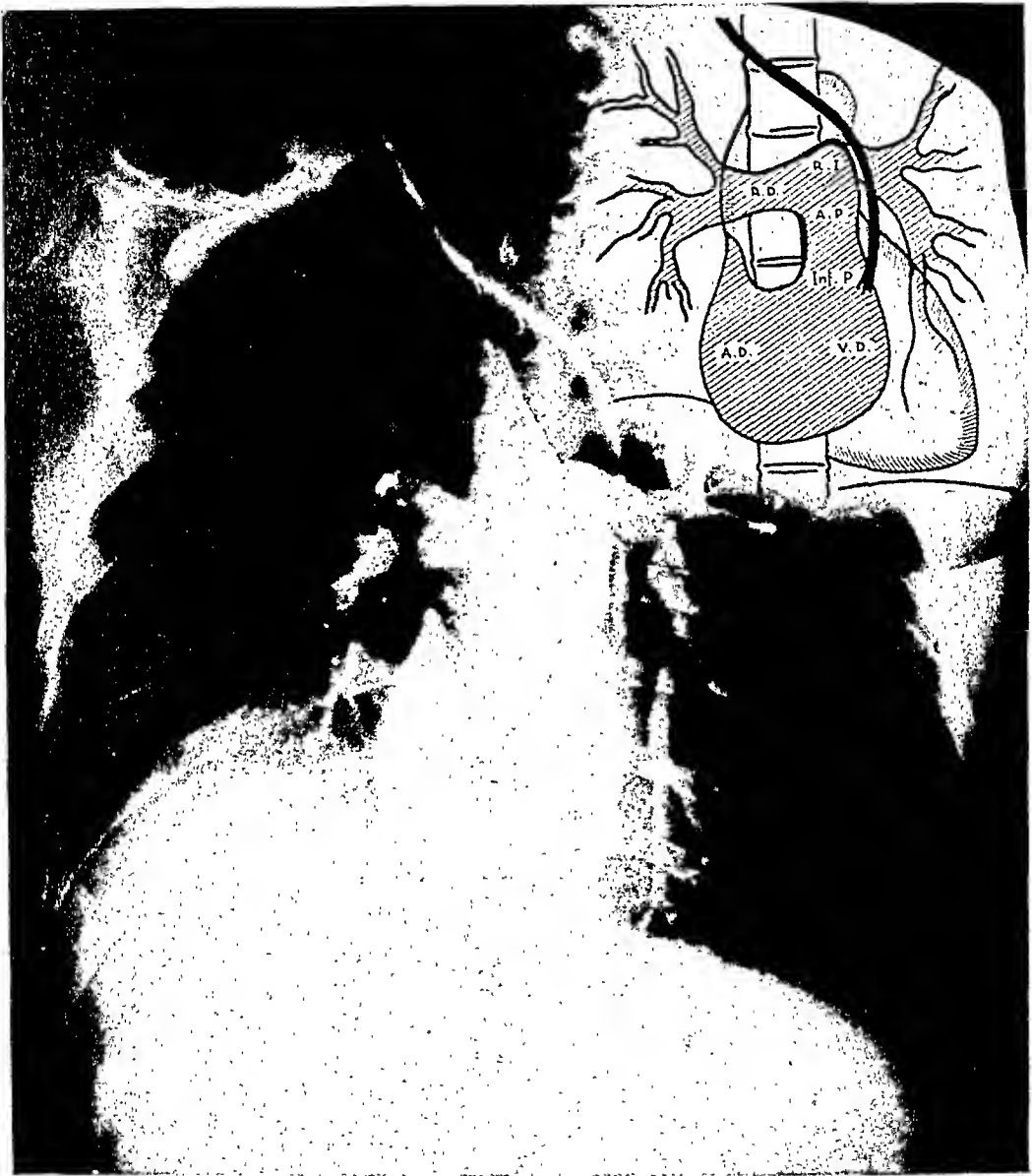


Fig. 5.—Same case as shown in Figs. 2, 3, and 4. Pulmonary arteries and right branches are particularly shown.



Fig. 6.—Angiocardiogram of right chambers of normal heart made in the lateral position.

widened and forms the shadow of the right atrium, which has a more or less oval shape in this projection. It is continued anteriorly by the inflow tract of the right ventricle which is visible in this projection. Ventrally there is the outflow tract of the right ventricle, which rapidly assumes an upward course



Fig. 7.—Angiocardiogram of normal right chambers and pulmonary artery. Lateral view.

until it joins the pulmonary artery itself. The diameter of the outflow tract of the right ventricle is about the same as that of the pulmonary artery. Between them, in the lateral position, are frequently seen the notches described in the frontal position, which we think are due to the pulmonary sigmoid valves (Fig. 7).

Beyond this notch the pulmonary artery takes a dorsal direction and divides into two branches, the right and left, which in turn divide into secondary branches. Quite often the opaque substance goes into the inferior vena cava (Fig. 8). The image of the injected right heart and the inferior vena cava resembles a sickle. When the opaque substance does not go as far as the inferior vena cava the image has a crescent shape. Castellanos calls this the "retort picture," since it recalls a well-known laboratory tool.



Fig. 8.—Angiocardiogram of normal right chambers and pulmonary artery. Lateral view. Note the filling of inferior vena cava.

IMAGE OF THE LEFT CAVITIES AND THE AORTA

If films are made a few seconds later, the pulmonary veins will be seen. These veins originate in the alveoli, and become more voluminous as they approach the left atrium. There are two pulmonary veins on the right side and two on the left. Two are situated cephalad, and two caudad. The left atrium soon becomes opaque (Fig. 9). Its shape resembles an "ace of spades," the apex

pointing caudad and to the left. Its shadow is superimposed on that of the vertebral column and corresponds more or less to the unfilled space of the right cavities, projecting between their limbs. Its left border is quite far from the heart's left border. The right side of the left atrium comes very near to the right



Fig. 9.—Angiocardiogram of normal left chambers. The left atrium is filled (see text).

border of the heart and very frequently the highest part of the right cardiac border is formed by the left atrium and not by the right. This fact makes it easy to understand why an enlarged left atrium frequently forms a double contour on the right side of the cardiac silhouette and why it infrequently forms a part of the left border of the cardiac silhouette. The filling of the left ventricle with the opaque substance also produces an oval shadow which is continuous

with the shadow of the left atrium, and extends as far as the apex of the heart. It is very common to see a deep notch between the left atrium and the ventricle. If we consider the picture of the atrium and the ventricle together they resemble roughly a figure eight.

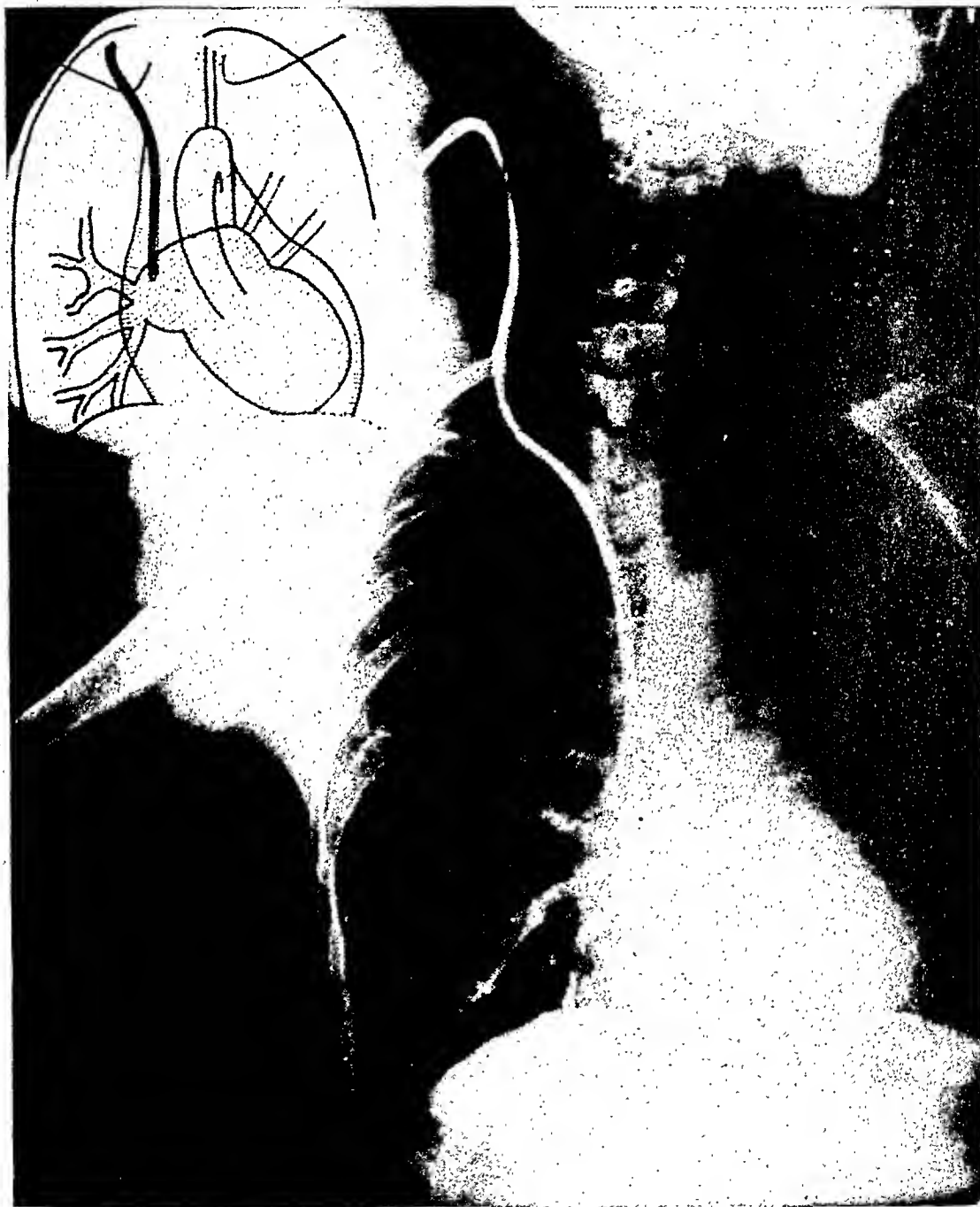


Fig. 10.—Angiocardiogram made in systole (see text).

This picture is obtained when we catch the heart in diastole but it varies when the film is made during systole. In the latter case the aorta is completely filled; there is no filling of the left ventricle and usually, but not always, there remains some radiopaque substance in the left atrium. We have already pointed

out that the right ventricle is always visible, though its shape will vary in films taken during diastole and systole. The left ventricle usually empties completely during systole. A film made in systole will show the aorta to be completely filled but the left ventricle will not be visualized, unless there is some pathologic circumstance which causes part of the substance to be retained (Fig. 10).

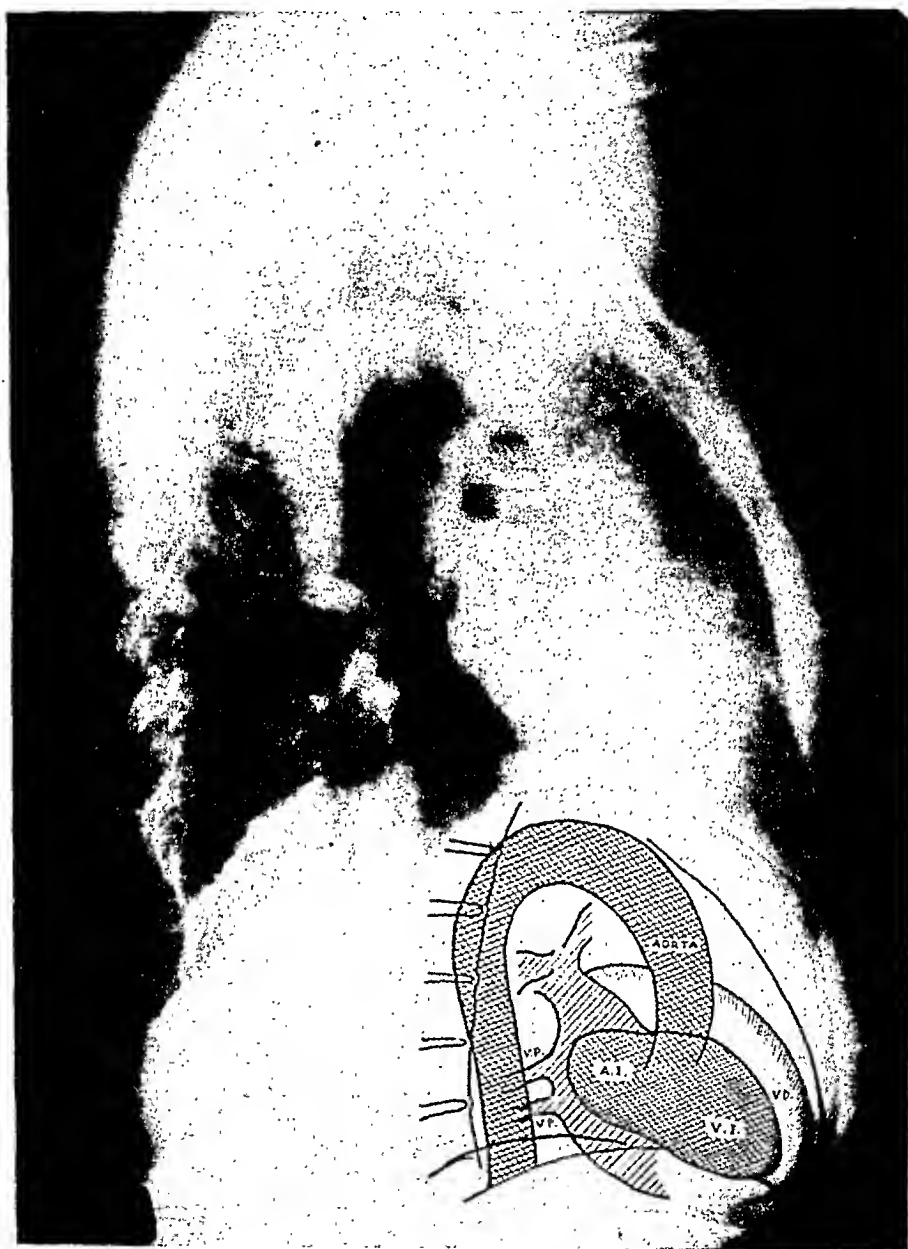


Fig. 11.—Angiocardiogram made in the lateral position. In this position the left chambers are not well visualized; the aorta and the pulmonary arteries are well visualized.

The complete filling of the left ventricle makes it possible to appreciate the location of the interventricular septum and in many cases the thickness of the ventricle wall. On the other hand, the inflow and the outflow tracts of the left

ventricle cannot be differentiated as they can be in the right ventricle; there is no demarcation between them.



Fig. 12.—Angiocardiogram of normal left chambers made in the lateral position. A notch marking the position of the aortic valves and a dilatation indicating the position of the sinuses of Valsalva are often seen (see text).

In the same anteroposterior projection the aorta is well visualized. It usually leaves the left ventricle at the level of the projection of the left border of the vertebral column. When the left ventricle is empty and the left atrium

still contains radiopaque substance, the aorta appears to come out from the left border of the atrium. Then it ascends more or less rapidly, depending on the shape of the heart, and then turns downward. The full descending aorta, the innominate artery, the two main carotids, and, lower down, sometimes the intercostal arteries can be visualized. Occasionally the completely filled renal arteries are seen.

The lateral projection (Fig. 11) is not very useful for visualizing the left chambers but it is useful for visualizing the pulmonary artery and the aorta; these structures are better seen in this position than in any other. The chambers of the left heart in this position are small. In the lateral projection the left chambers as a whole also resemble a figure eight. The aorta can be seen coming out from the left ventricle at about the upper loop of the figure eight; it rapidly ascends and is quite near the anterior chest wall. At this point an anterior and a posterior notch very similar to those seen in the pulmonary artery can be seen (Fig. 12). Immediately above the notch there is a slight dilatation. We think that the notch is due to the sigmoid valves and the dilatation to the sinuses of Valsalva. The situation of the aorta naturally varies according to the shape of the chest and to the age of the subject: in older people it is not so near the chest wall.

ABNORMAL IMAGES

In order to clarify description and to facilitate comparison with the normal images, we shall describe the pathologic images which will be described in the same order that has been used in describing normal hearts. The structures

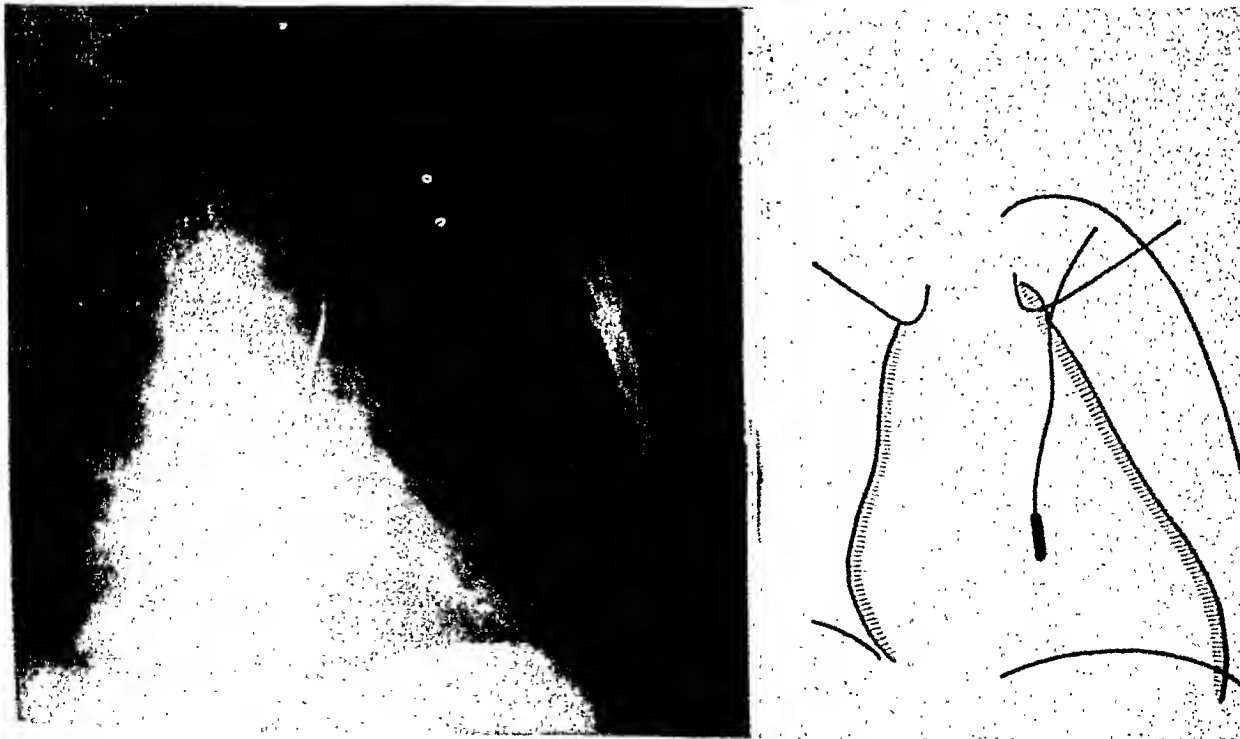


Fig. 13.—Angiocardiogram of a patient with persistent left superior vena cava.

and chambers will be discussed in the order on which they are visualized after the injection of the opaque substance. Two main contingencies may be present: (1) the substance may follow the normal circuit; or (2) it may follow an anomalous course, because of perforations of the septa, or the vessels do not have normal origins or connections, or there are abnormal communications between the vessels.

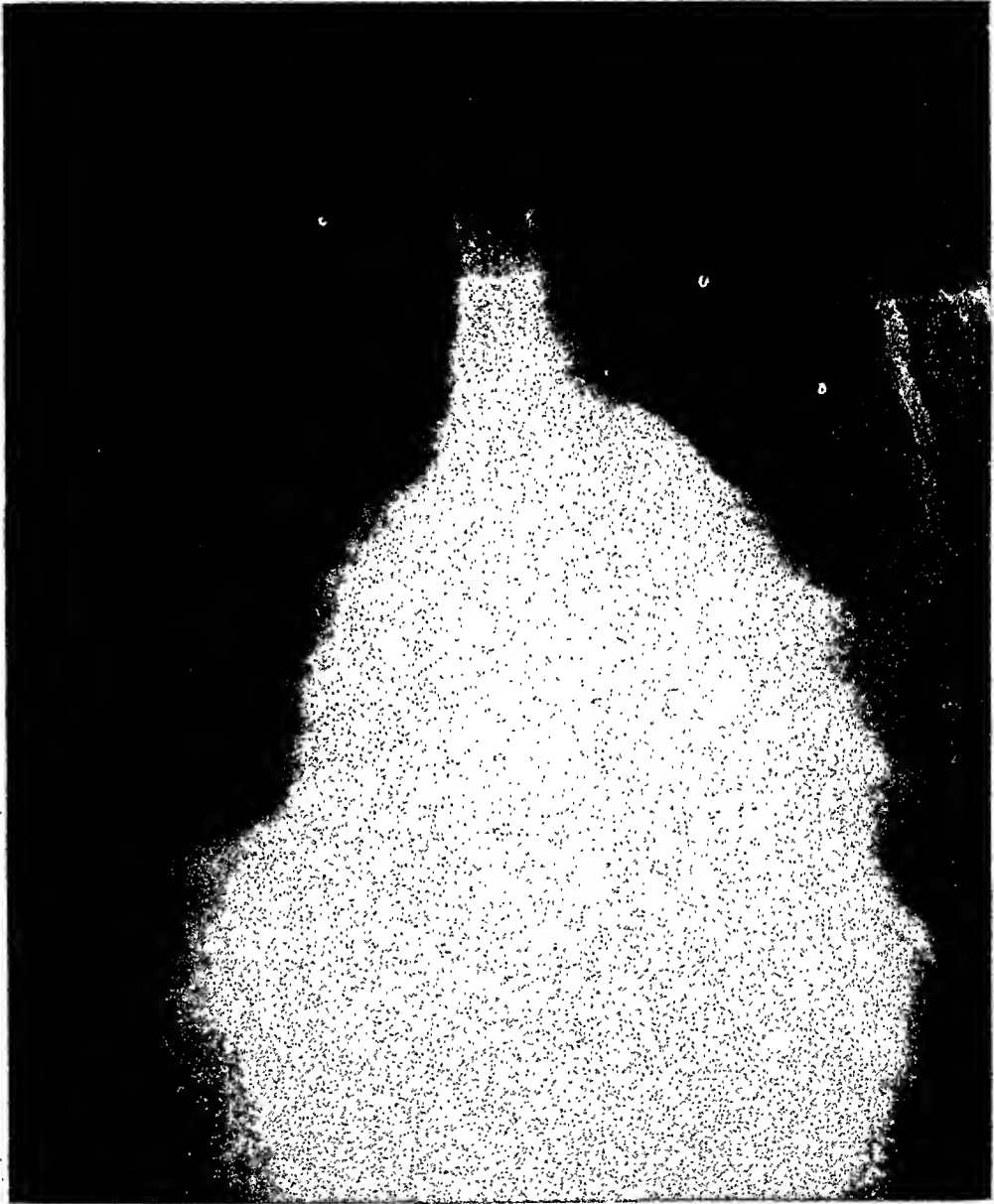


Fig. 14.—Ordinary x-ray film of patient with mitral and tricuspid stenosis.

Abnormal Images With Normal Routes of Flow.—The image of the *superior vena cava* is always perceptible. In most instances the injecting catheter is inserted into this vessel. Even when it is not possible to catheterize it, and when the injection has to be made into the jugular vein with a large-gauge needle, the presence of the opaque substance makes possible the identification of the *vena cava* and the recognition of anomalies of this vessel. Fig. 13 shows a persistent left *superior vena cava* which is probably connected directly to the left

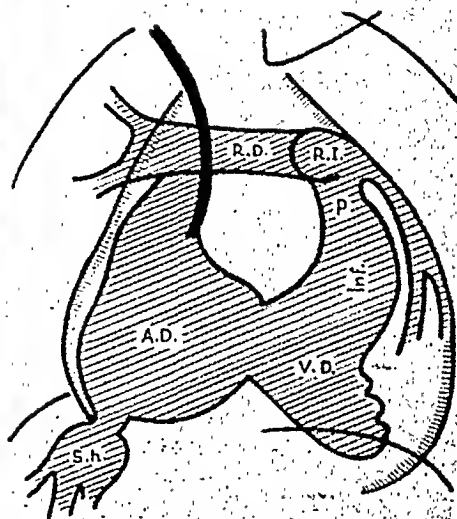
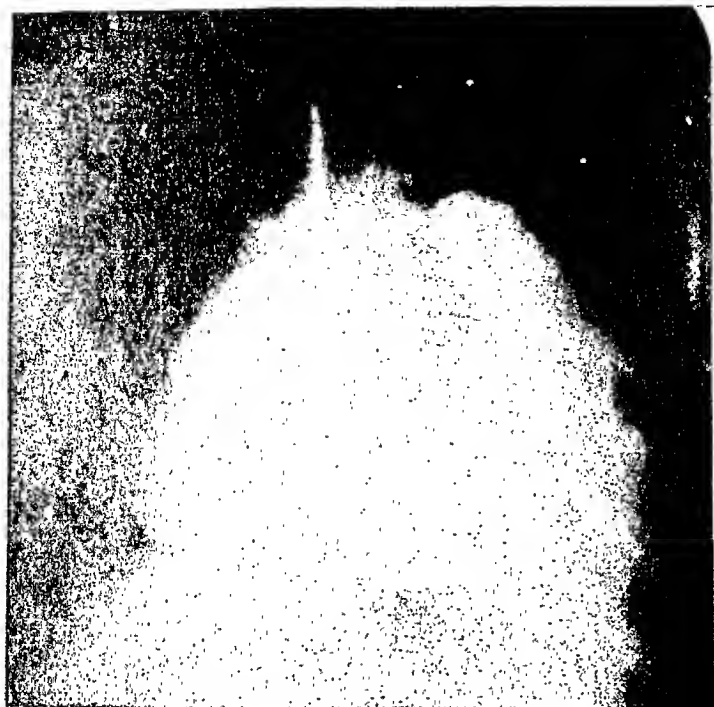


Fig. 15. — Angiocardiogram of same case shown in Fig. 14 (see text).

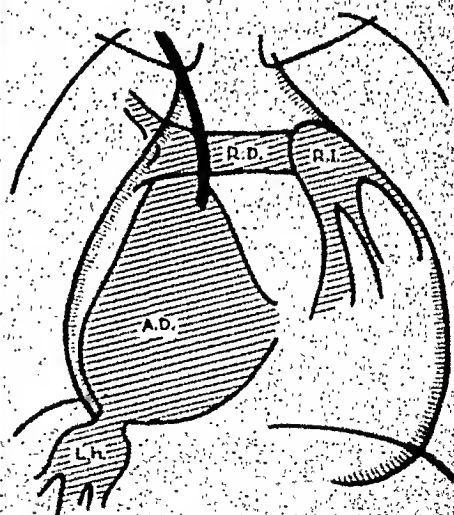


Fig. 16. — Angiocardiogram of same case shown in Figs. 14 and 15 (see text).

auricle. The electrocardiogram that was recorded indicated that the catheter which contained the electrode probably entered the right ventricle.

The *right auricle* is seldom seen as an isolated chamber. Since it empties promptly into the ventricle, the image obtained usually shows both cavities together. It is possible to see the auricle alone, however, when the ventricle empties and the auricle remains full; this is often the case in tricuspid stenosis, (Fig. 14). Here is an ordinary x-ray of a patient with rheumatic mitral disease and with a marked dilatation of the cavities. The angiocardigram (Fig. 15)

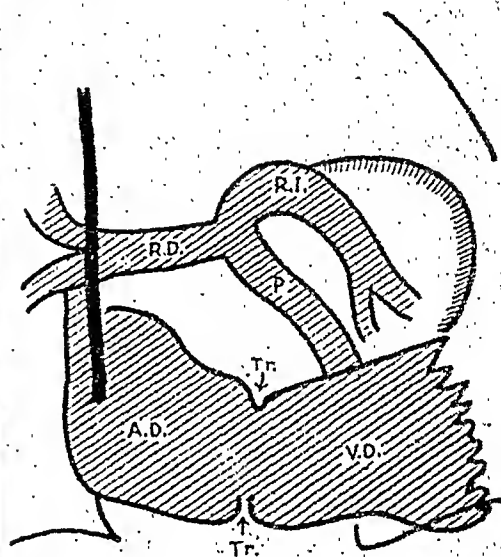


Fig. 17. — Angiocardigram of a patient with an aortic aneurysm which compressed the infundibulum of the pulmonary arteries. A notch caused by the tricuspid valve is seen.

at the end of the injection shows an enormous right auricle, clearly separated from the ventricle by a narrow zone corresponding to the tricuspid valve. In Fig. 15, however, the right ventricle is full, as well as the two branches of the pulmonary artery; but three seconds later, (Fig. 16), the ventricle has emptied while the auricle still retains the opaque substance: it remained full six and even ten seconds after the injection, when the aorta was already completely visible. The diagnosis of tricuspid stenosis in this case had escaped the clinical examination.

The image of the *right ventricle* may be missing or it may be greater than normal or, finally, it may show deformations. We shall discuss later the cases where it is not seen, since they depend upon complex malformations. Fig. 17 is a good example of an exaggerated enlargement of this cavity; it is prolonged

as far as the apex and reaches the left border of the heart, in contrast to a narrow and elongated expulsion chamber. The left branch of the pulmonary artery is clearly visible. This film was obtained from a patient with an aortic aneurism which compressed the region of the pulmonary infundibulum. In this same plate the notch marking the site of the tricuspid valve is seen. To the best of our knowledge this is the first time that this structure has been visualized.



Fig. 18.—An ordinary x-ray film of a patient with mitral stenosis.

We have also found this image of dilatation of the main *trunk of the pulmonary artery* and of its branches, and diminished size of the infundibulum in the course of rheumatic mitral stenosis, with no clinical sign to make us suppose that there was either a narrowing or a compression of the infundibulum. Fig. 18 corresponds to an ordinary mitral silhouette. The patient had a classical stenosing valvulitis. The protuberance which deforms the medial arc makes us suspect that there is a greatly dilated left pulmonary branch. Actually, three seconds after the injection (Fig. 19), the trunk of the artery and its left branch are seen to be very

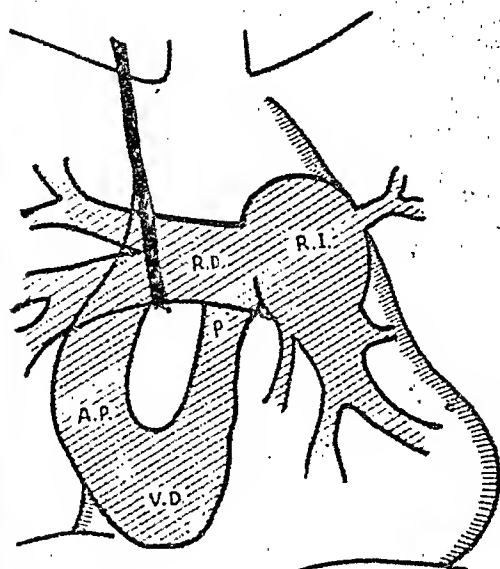


Fig. 19.—Angiocardiogram of same case shown in Fig. 18 (see text).

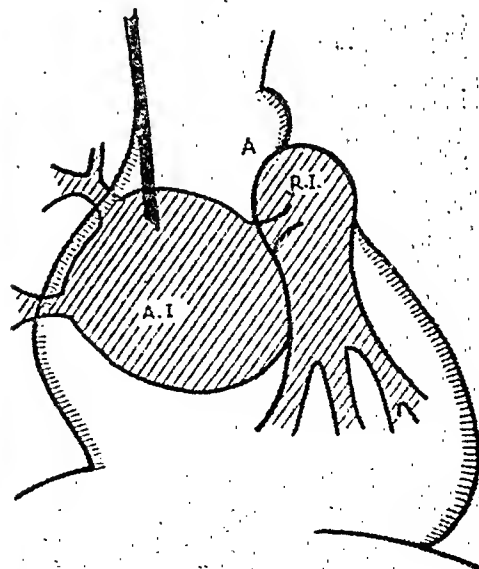


Fig. 20.—Angiocardiogram of same case shown in Figs. 18 and 19 (see text).

dilated. The infundibulum, on the other hand, can not be seen. Six seconds after the injection, the pulmonary and infundibular images are similar, and even three seconds later the arteries are still opaque (Fig. 20), although the left auricle is full. This plate provides a beautiful visualization of the isolated *left auricle*, only slightly enlarged but with a clear lower limit which corresponds to the mitral valve.

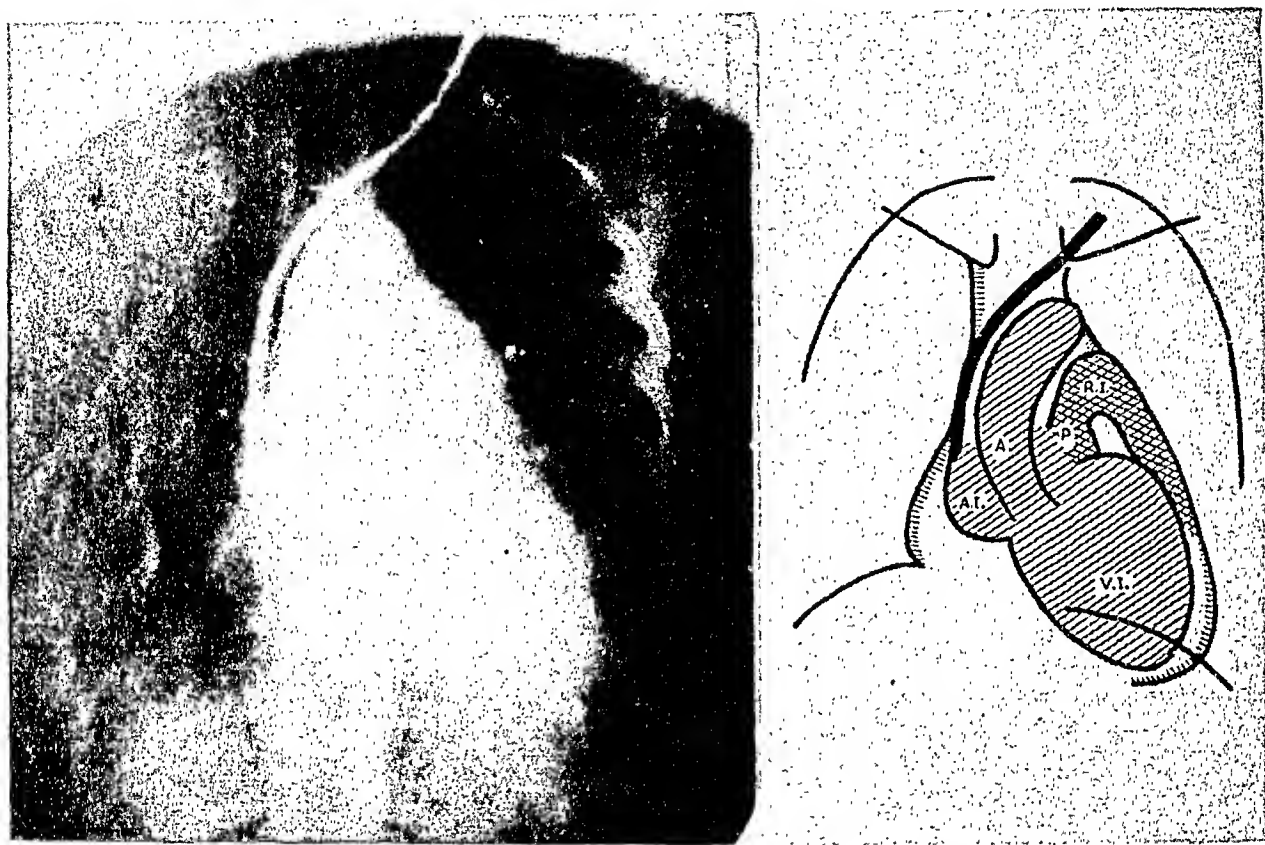


Fig. 21.—Angiocardiogram of patient with patent ductus arteriosus. The opacity of the pulmonary artery is maintained until the aorta is filled.

Regarding the left cavities, the most common occurrence is to find both chambers full at the same time. A marked enlargement of the *left ventricle* is clearly shown in Fig. 21. In this case an undiagnosed condition maintained the filling of the pulmonary artery up to the time of the filling of the aorta. This fact, as we shall see later, strongly suggests a persistence of the ductus arteriosus.

Angiocardiography yields very beautiful plates of the aorta and allows diagnosis to be made which may not be reached otherwise. A typical example is that of the case shown in Fig. 22, a simple x-ray film which shows an enormous prominence of the medial arc and a moderate cardiac enlargement of the right-sided type. The image strongly suggests an aneurysm, either of the pulmonary artery or of the aorta at the sinus of Valsalva. The clinical problem was not

easy. The patient, a 45-year-old man, had syphilis. The precordial region bulged slightly at its base, and there was a double beat. A slight systolic murmur and a somewhat louder diastolic murmur could be heard in the third left intercostal space. The radial pulse, however, was not of the collapsing type. Furthermore, the enlargement was of the right and not of the left cavities. The injection



Fig. 22.—An ordinary x-ray film of a patient with an aneurysm of the left sinus of Valsalva which compressed the pulmonary infundibulum.

of opaque substance eliminated all doubts, (Fig. 23). At its end, the right cavities and the pulmonary artery with its branches were filled: The bulge, however, had not changed. The right cavities were clearly dilated and did not empty, either in four or in eight seconds, thus demonstrating the presence of an obstruction. When after twelve seconds they did empty (Fig. 24), the left ventricle and also the aneurysmal pocket and the descending aorta were seen to

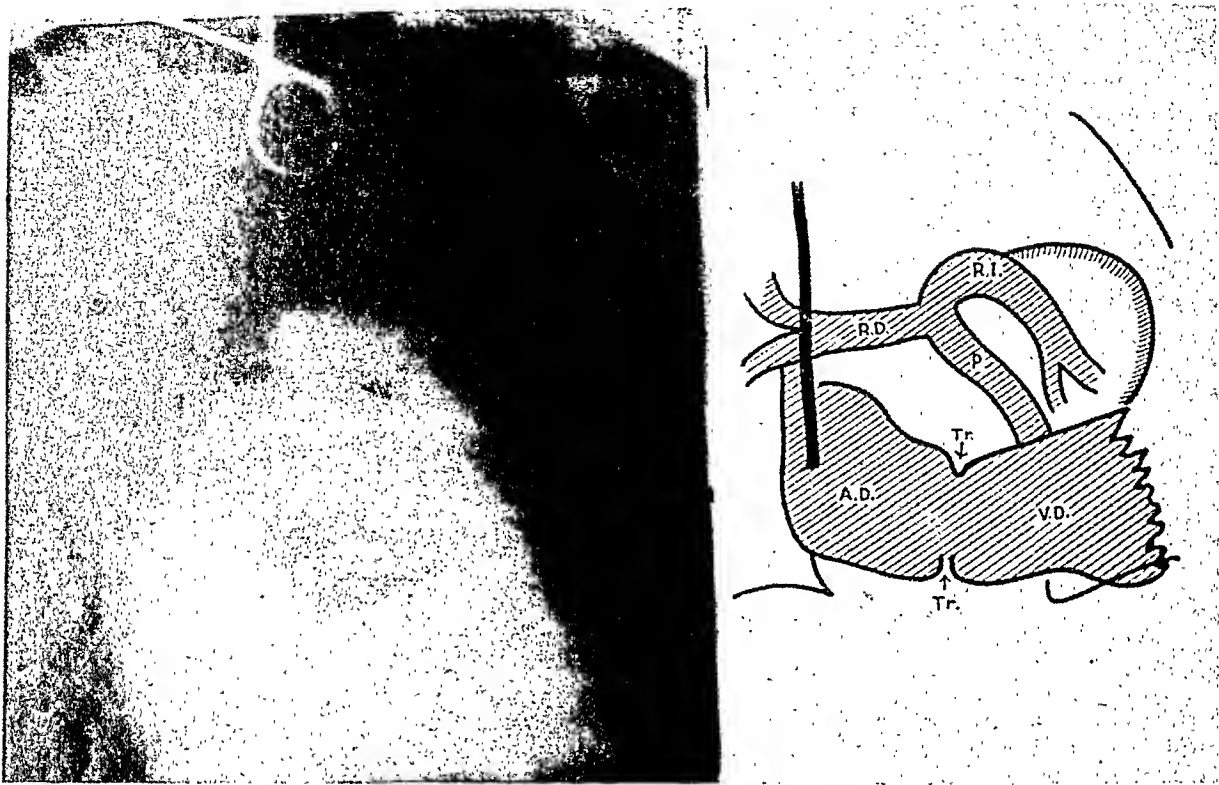


Fig. 23.—Angiocardiogram of same case shown in Fig. 22 (see text).

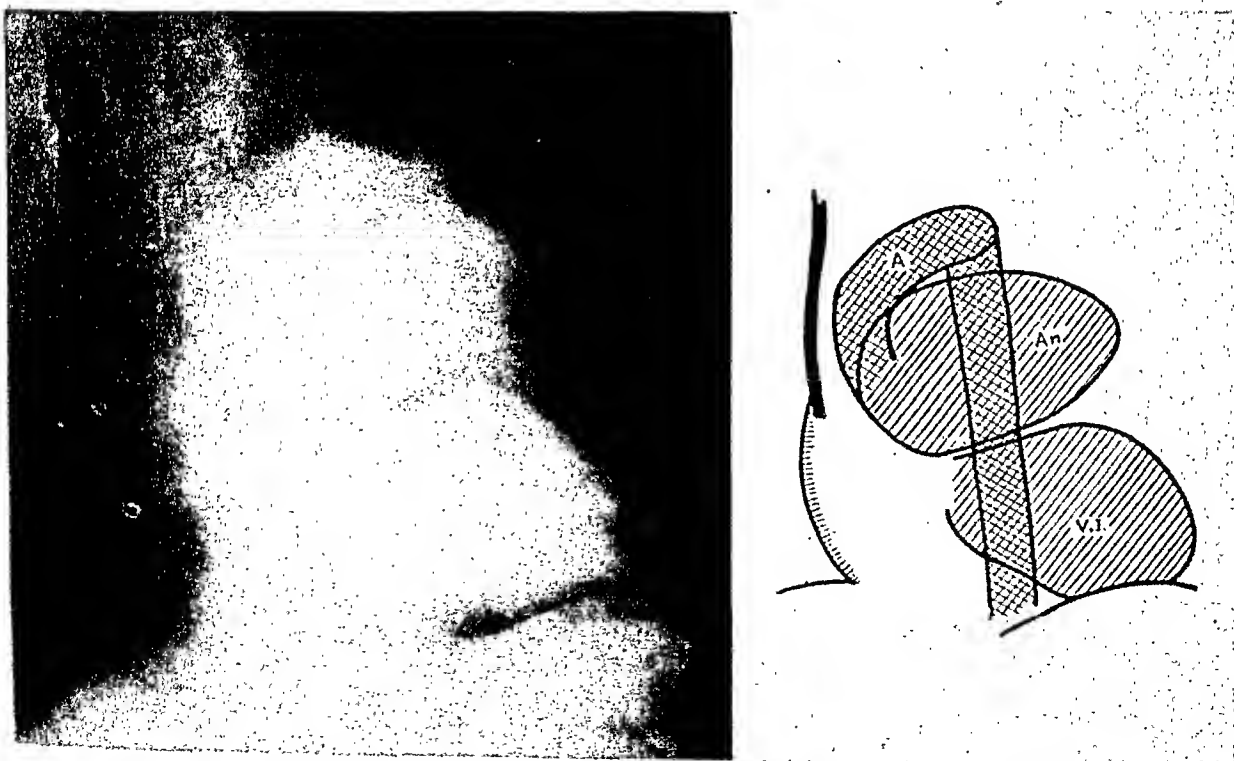


Fig. 24.—Angiocardiogram of same case shown in Figs. 22 and 23 (see text).

be filled. The diagnosis of *aortic aneurysm* of the left sinus of Valsalva with compression of the pulmonary infundibulum could be established with certainty.*

Not less interesting is the contribution of the method to cases of *isthmus stenosis* or *coarctation of the aorta*. In the ordinary x-ray film (Fig. 26), taken with a Bucky diaphragm and at a short distance in order to demonstrate Roesler's

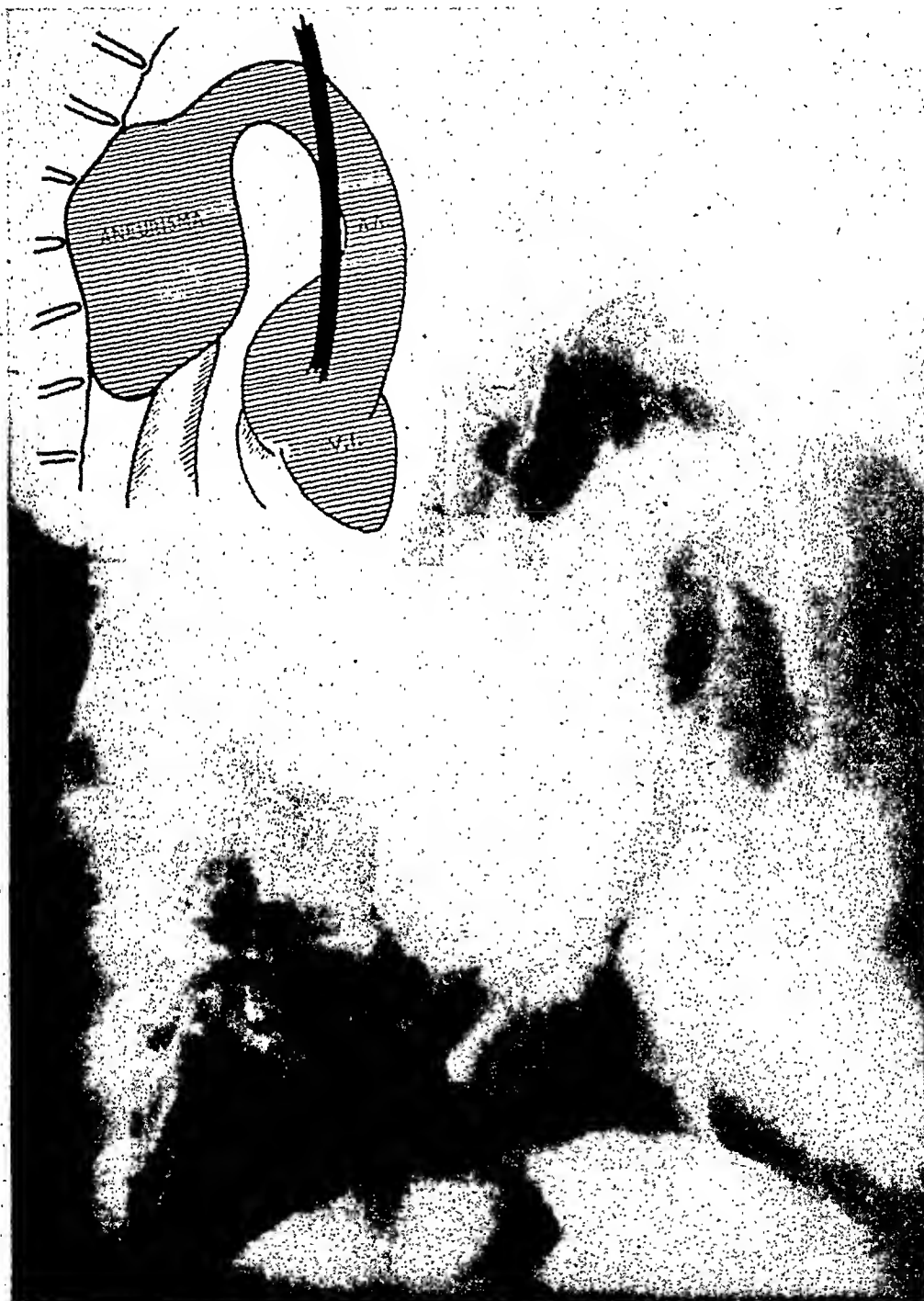


Fig. 25.—Angiocardiogram of a patient with a huge aneurysm of the thoracic aorta.

*In another type of aortic aneurysm the differential diagnosis from tumors can be established with precision. Fig. 25 shows a huge aneurysm of the thoracic aorta. It would be very difficult to demonstrate this by any other means.

sign of costal erosion, a quasi-normal cardio-aortic silhouette is seen with only slight enlargement of the left ventricle (confirmed later by a teleroentgenogram). In the lateral position at the end of an injection (Fig. 27) a splendid normal image of the right cavities and of the pulmonary branches is seen. Four seconds later (Fig. 28), on the other hand, the left cavities likewise appear normal, except for a thick ventricular wall. The ascending aorta and the transverse and initial portion of the descending aorta are all filled with the opaque sub-

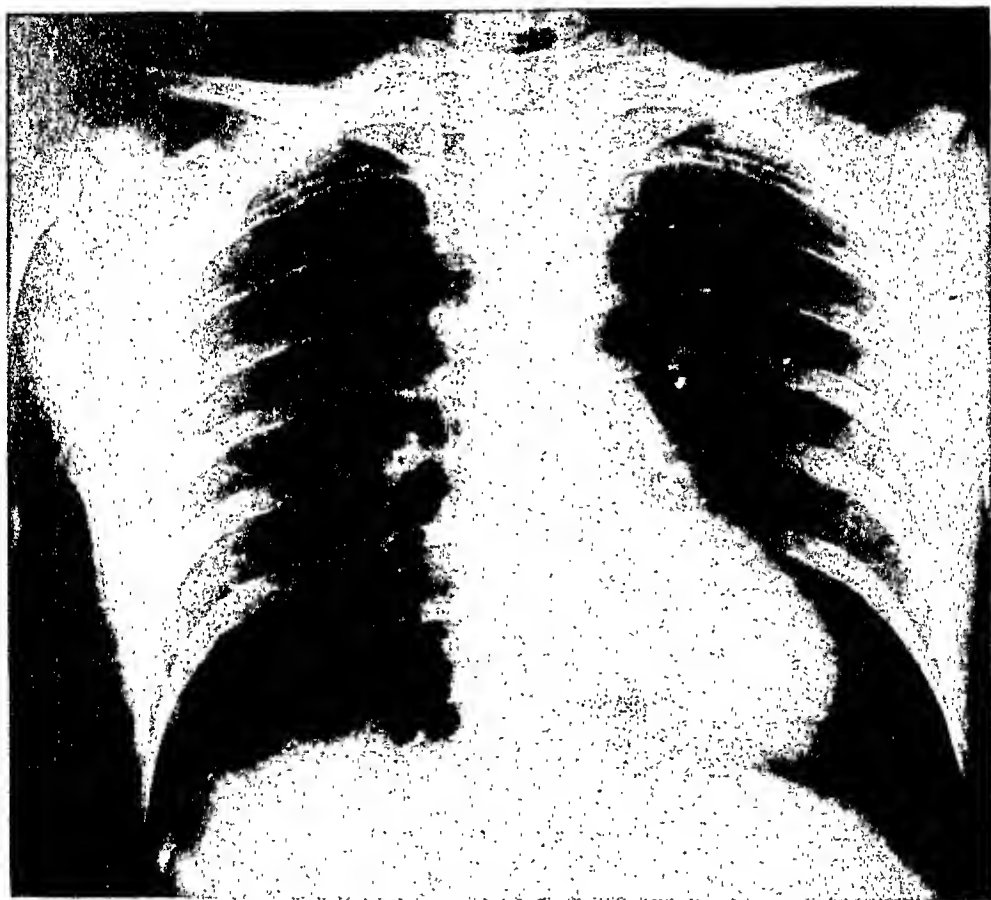


Fig. 26.—An ordinary x-ray film of a patient with a coarctation of the aorta.

stance up to the level of the intersection with the pulmonary artery. The six-second plate (Fig. 29) still shows a visible aortic arch and, also, a visible thoracic aorta. Between the two segments of the aorta there is a narrow zone, practically invisible and about 3 cm. long, where the two visualized segments approach each other by slender elongated tips. The narrowing is particularly noticeable in the image of the thoracic aorta, whose upper part is needlelike, and is followed immediately by a spindle-shaped dilatation about 6 cm. long, continued below by a narrow, hypoplastic aorta, which strongly contrasts with the wide ascending aorta.

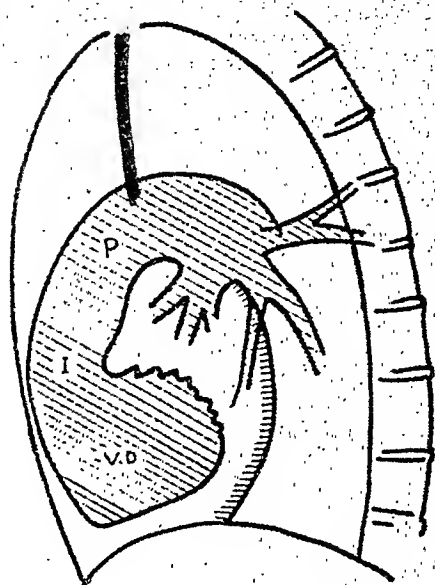


Fig. 27.—Angiocardiogram of same case shown in Fig. 26 (see text).

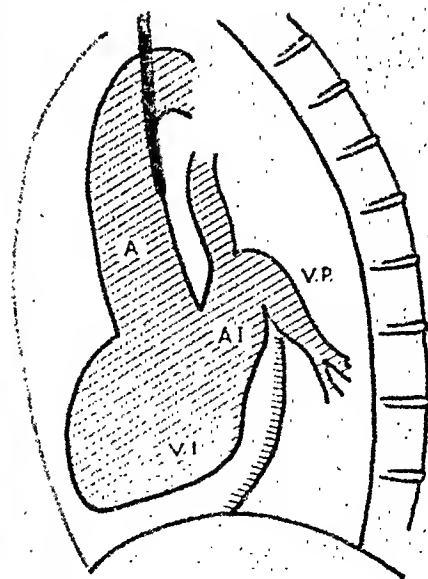


Fig. 28.—Angiocardiogram of same case shown in Figs. 26 and 27 (see text).

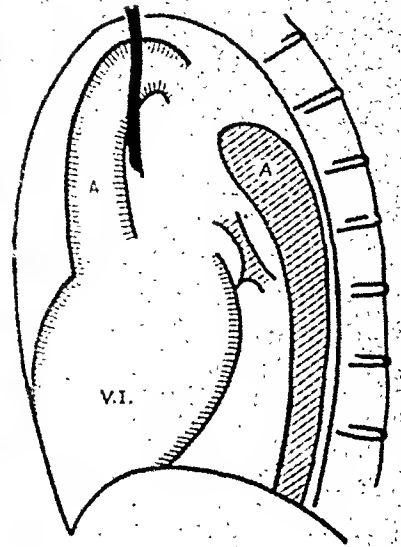


Fig. 29.—Angiocardiogram of same case shown in Figs. 26, 27, and 28 (see text).

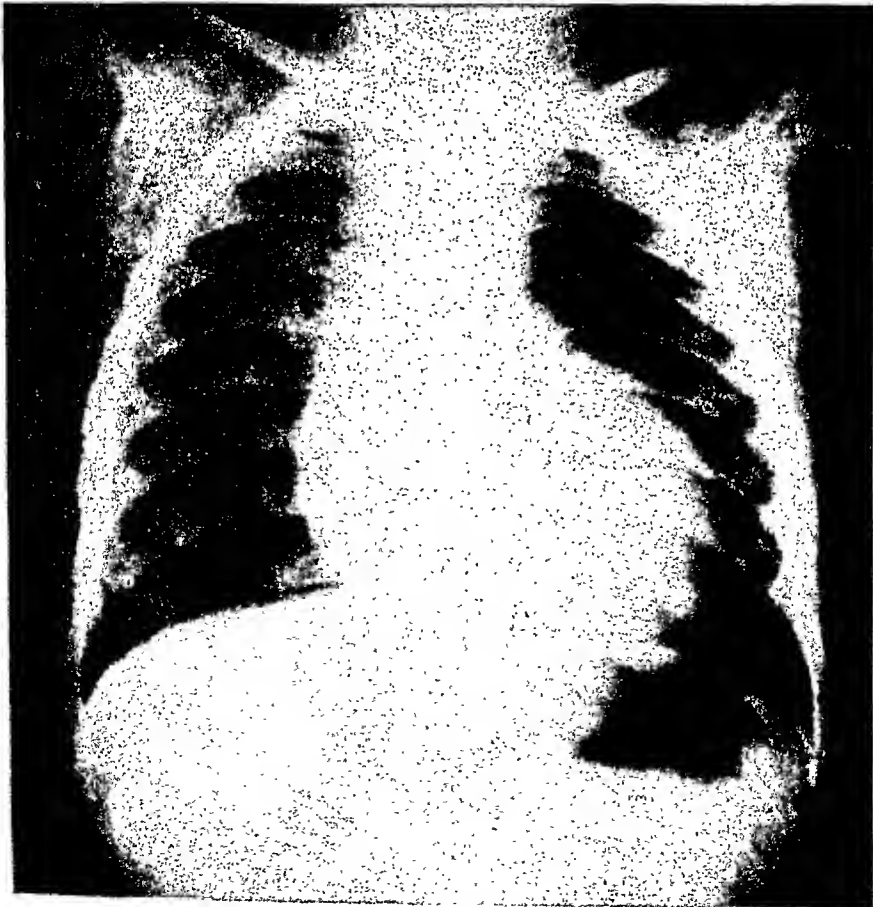


Fig. 30.—An ordinary x-ray film of a 4-year-old child with cor biloculare or cor triloculare biatriatum with a persistence of a single arterial trunk.

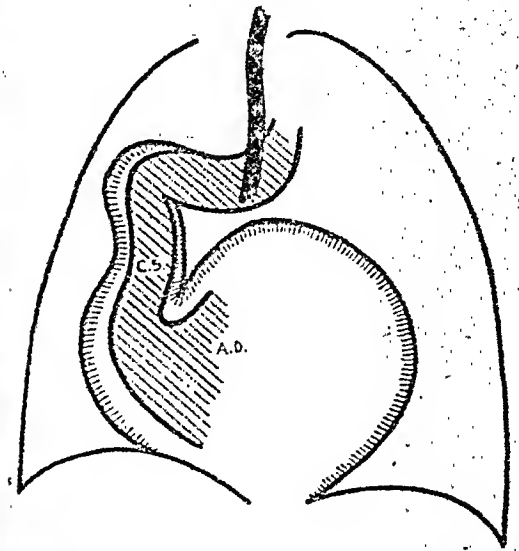


Fig. 31.—Angiocardiogram of same case shown in Fig. 30 (see text).

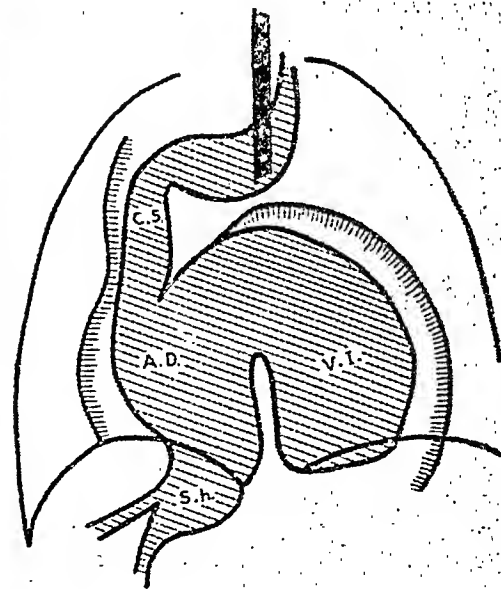


Fig. 32.—Angiocardiogram of same case shown in Figs. 30 and 31 (see text).

The films which we have described constitute, so far as we know, the first visualization of aortic coarctation that has been obtained in clinical medicine. This method gives valuable information concerning the site, degree, and extent of stenosis.

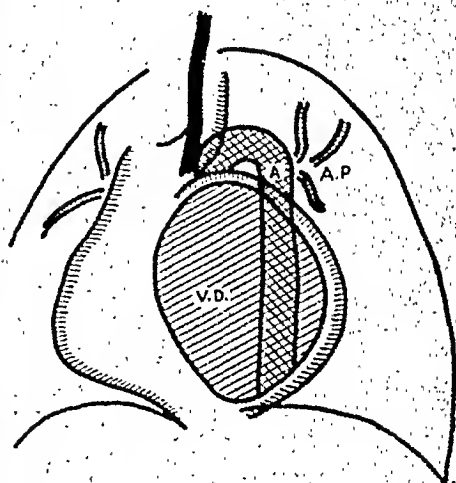
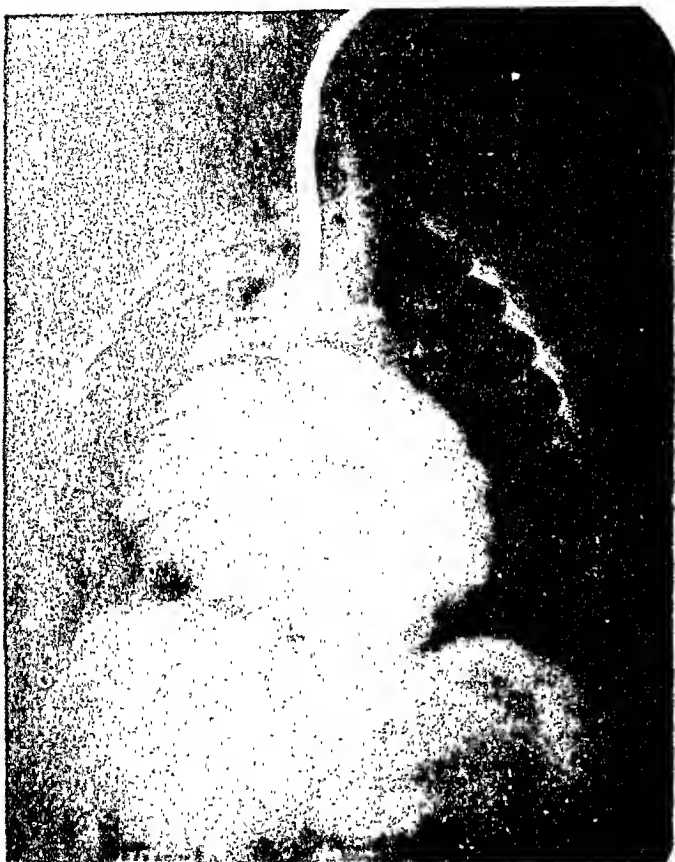


Fig. 33.—Angiocardiogram of same case shown in Figs. 30, 31, and 32 (see text).

Abnormal Images With Abnormal Routes of Flow.—It is in this field that the angiocardiographic method is of greatest value. It provides the only way of visualizing congenital abnormalities and atypical connections between the two circulations. The current of opaque substance may be followed through its abnormal route.

The patient whose film is shown in Fig. 30 is a 4-year-old child with congenital syphilis. He was intensely cyanotic and incapable of any effort. The heart was large. A systolic murmur, weak and somewhat musical, could be heard in the second left intercostal space and was transmitted to the vessels of the neck. The ordinary x-ray film shows marked enlargement of the left ventricle, a broad vascular pedicle, and an almost total lack of pulmonary trabeculae and vascular branches. Halfway through the injection (Fig. 31) the superior cava is visualized and appears large and displaced toward the right; its continuity with the right auricle is clear. One second later (Fig. 32), at the end of the injection, the right auricle is full as are the suprahepatic veins; but the left auricle and ventricle become filled at the same time. Still another second later (Fig. 33), the auricles

are already empty and only the enormous left ventricle, from which springs a narrow aorta, can be seen. At no instant was it possible to detect the right ventricle or the pulmonary artery. The few pulmonary vessels observed were seen to fill simultaneously with the aorta.



Fig. 34.—An ordinary x-ray film of a 4-year-old child with tricuspid atresia and cor triloculare with persistence of the truncus arteriosus.

The angiocardigraphic data are eloquent: there is no right ventricle and no pulmonary artery, and both auricles are amply connected. The left ventricle is isolated and enormous. Clearly there exists a *cor biloculare*, or at most a *cor triloculare biatriatum*, with persistence of a single arterial trunk.

A somewhat similar case (Fig. 34) is that of another 4-year-old boy, very cyanotic since birth and with a soft systolic thrill and a harsh and loud systolic murmur at the second left intercostal space. The picture suggested a complex malformation with stenosis of the pulmonary artery, perhaps a tetralogy of

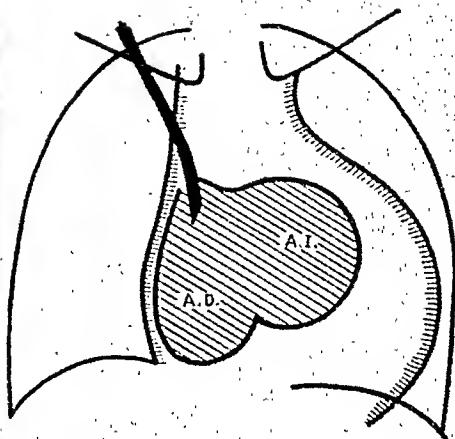


Fig. 35.—Angiocardiogram of same case shown in Fig. 34 (see text).

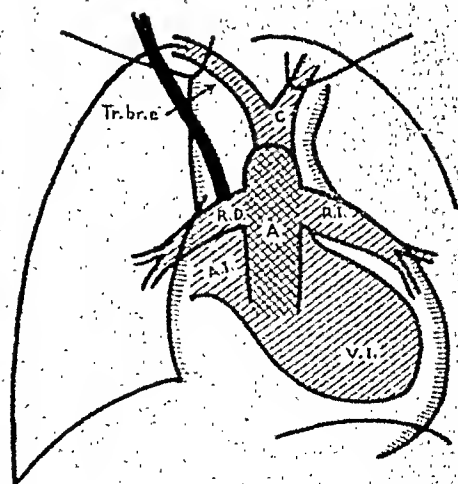


Fig. 36.—Angiocardiogram of same case shown in Figs. 34 and 35 (see text).

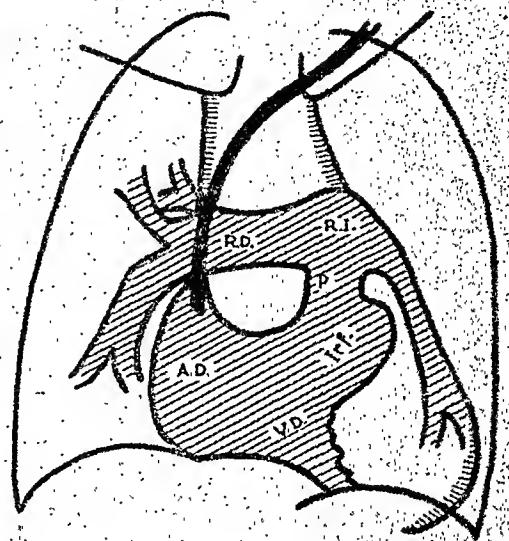


Fig. 37.—Angiocardiogram of patient with patent ductus arteriosus.

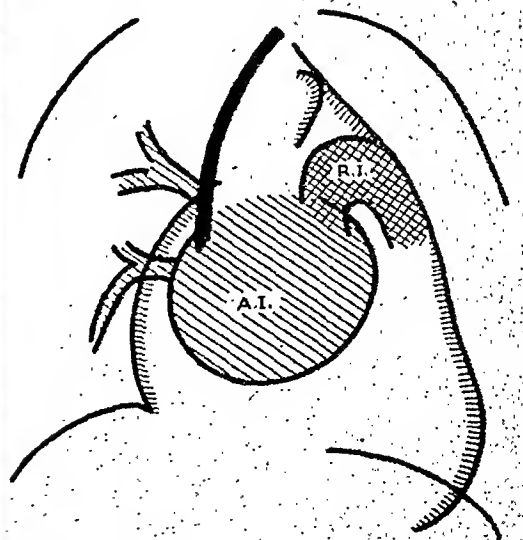
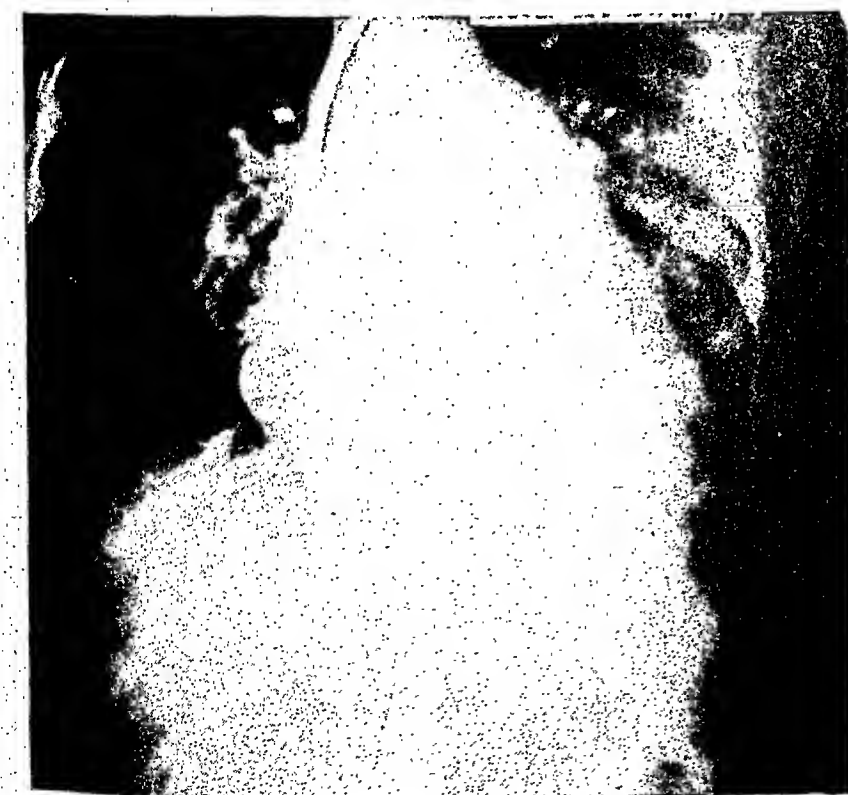


Fig. 38.—Angiocardiogram of same case shown in Fig. 37 (see text).

Fallot. Halfway through the injection (Fig. 35), both auricles are visualized and appear full and connected with each other, but separated by a clear notch. Subsequent plates, taken at one-second intervals, show a very hypertrophied left ventricle which fills first, and is then followed by filling of the aorta (Fig. 36). The left ventricle occupies a medial position and gives rise to two pulmonary branches. At no time was an image of the right ventricle obtained. These findings indicated a diagnosis of *tricuspid atresia* and *cor triloculare* with *persistence of the truncus arteriosus* instead of Fallot's tetralogy, which had appeared certain.

When Fallot's malformation or Roger's disease is actually present, the images are conclusive. Since we have studied mainly adults, we do not yet have any images of our own. The beautiful plates obtained by Castellanos⁶⁻⁸ with his own methods may be consulted.



Fig. 39.—Angiocardiogram of same case shown in Figs. 37 and 38 (see text).

Finally, a new contribution of the method we are recommending and are presenting for the first time is its aid in diagnosing *patent ductus arteriosus*. It is not possible, of course, to visualize the duct itself, since it is usually so short that even the surgeon has difficulty in seeing it. The evidences of its existence are indirect. In Fig. 37, at the end of the injection, the right cavities are seen to be normal and full, with an accentuated prominence of the main trunk and the left branch of the pulmonary artery. Two seconds later, the pulmonary vessels are still full and the left auricle begins to appear. Two seconds later still (Fig. 38), the left auricle is clear and the left ventricle is beginning to fill. The opacity

of the pulmonary artery decreases from one plate to another. But in the next plate (Fig. 39), taken six seconds after the injection, in which the left ventricle as well as the aorta are totally opaque, the trunk and branches of the pulmonary artery, instead of completing the emptying initiated in the previous plates, again become opaque. This delayed back-flow filling of the pulmonary artery, at the time that the aorta fills, is a decisive radiologic sign: it is only possible if there is a fistulous connection between the two vessels. It is unnecessary to emphasize the importance of this sign in doubtful cases, especially now that this diagnosis carries with it the practical implication of surgical intervention.

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THE SUBSTITUTION OF A TETRAHEDRON FOR THE EINTHOVEN TRIANGLE

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THE early studies of the electrical phenomena associated with the human heartbeat carried out by Waller and by Einthoven and his associates led to the adoption of the leads from the two arms and the left leg which are still in universal use. For a great many years little thought was given to the possibility that these leads might be entirely inadequate in certain respects and that great progress in electrocardiographic diagnosis might be achieved by supplementing them with leads of other kinds. Some fifteen years ago, however, it became evident that leads in which one electrode is placed on the precordium and the other on some part of the body much farther from the heart are, to some extent, similar to unipolar leads from the ventricular surface, such as were used by Lewis and Rothschild,¹ and are capable of yielding information which limb leads cannot give. In the last decade, precordial leads have become indispensable.

This sequence of events raises the question as to whether further important advances in electrocardiography are likely to result from the development of still other new leads. If, like our predecessors, we may be overlooking opportunities in this direction, it is worth while to examine our present situation in the hope of ascertaining how we should proceed in order to take advantage of any such that may exist.

The general character of the heart's electrical field and the main features of the relations between it and the rise and decline of the excitatory process were clearly understood by Waller, by Einthoven, and by some of their contemporaries. These pioneers realized that, for certain purposes, the electromotive force of the heart may be regarded as a vector and that the limb leads are poorly suited to the study of the cardioelectric forces which are perpendicular to the plane defined by them. They knew also that these leads, unlike those from electrodes in contact with the heart's surface, yield a kind of average electrocardiogram which cannot be expected to depict variations in the excitatory process that involve only a small region of cardiac muscle and leave the general course of myocardial activation and recovery unchanged. At the start, it was, however, naturally difficult to interpret experiments in which direct leads from the ventricular surface were employed; the more so because of the inconstancy and variability of the form of the ventricular complex encountered in leads of this kind. These

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variations were troublesome even though the factors responsible for them were understood. This probably explains why indirect leads came to be preferred to direct leads in experiments on animals in which the latter would have been much more useful.

The history of the development of our knowledge of electrocardiographic leads indicates that two courses are open to us in our attempts to find better methods of leading than we now possess. The first is to search for additional leads akin to unipolar precordial leads. These may be regarded as semidirect leads from the anterior ventricular surface. Such leads have a particularly favorable spatial relation to the cardiac muscle nearest the exploring electrode and they are capable of detecting lesions affecting it which are far outside the reach of any lead or combination of leads from electrodes that are distant from the heart. On the other hand, they are clearly unsuitable for discovering lesions so located that the exploring electrode cannot be placed much closer to them than to more normal parts of the myocardium. Since a semidirect lead from one cardiac region is necessarily an indirect lead from others, it is obvious that an adequate study of the whole heart by this method must involve the use of many leads. A relatively small exploring electrode must also be employed, for if a large one is used, the advantages gained by putting it close to the heart are lost through its short-circuiting effect.

Unfortunately, most of the epicardial surface is not accessible to exploration by semidirect leads. As far as the anterior ventricular surface is concerned, we can do fairly well by moving the exploring electrode step by step across the precordium, but the posterior ventricular surface is much farther from the skin so that unipolar leads from the back are far less effective than unipolar leads from the front of the chest. Unipolar esophageal leads are very useful for the purpose of studying certain auricular disturbances and often furnish important information in cases of posterior infarction. For the purpose of exploring all of the posterior ventricular wall they leave much to be desired. Worth-while information will certainly be gained by taking unipolar leads from the cavities of the right auricle and right ventricle which are accessible by catheterization. This procedure will surely prove a valuable one for research and may occasionally yield data of clinical value. On the whole, however, undeveloped possibilities of improving cardiac diagnosis through the exploration of additional parts of the epicardial surface by means of semidirect unipolar leads do not seem particularly promising.

The second course is to try to find the indirect leads that will give us the most useful over-all or average electrocardiograms with the full realization that such leads cannot be expected to supply information regarding abnormalities of the excitatory process that do not involve comparatively large regions of muscle. It is clear that the leads needed for this purpose will not be numerous so that the time required to take them will be small. The electrodes employed may be relatively large, and the use of such electrodes reduces to a minimum the difficulties due to the high resistance of the skin and to polarization. Neither the standard limb leads nor unipolar limb leads adequately meet our needs because they do not furnish sufficient information concerning variations in the excitatory

process affecting chiefly the sagittal components of the cardiac electromotive forces. By means of limb leads alone it is impossible to detect lesions confined to certain parts of the heart muscle and very difficult to differentiate peculiarities of the form of the electrocardiogram due to rotation of the heart about an axis that is nearly parallel to the frontal plane from those due to intrinsic cardiac disturbances.

Einthoven's early papers display his deep interest in the effects of rotation of the heart upon the electrocardiographic deflections and his method of finding the projection of the electrical axis of the heart upon the frontal plane was evidently an outgrowth of ideas that he had begun to develop years earlier. Many since his day have been equally conscious of this problem and have made important contributions bearing upon it. Nevertheless, much remains to be done. We have reached the stage where we know that rotation of the heart often has profound effects upon the form of the electrocardiogram which we have in the past attributed to other causes, but our ability to recognize these effects with certainty is still small.

The possibility of improving this situation by employing sagittal leads of one kind or another has occurred to many investigators. We regret that it is not possible to review the extensive literature on this subject. We shall refer only to the work of Arrighi,² of Buenos Aires. In his doctoral thesis, Arrighi analyzed a large series of tracings obtained by means of three leads which define a sagittal triangle. The apices of this triangle are a point on the left submaxillary region close to the chin, a point 3 or 4 cm. to the left of the midpoint of a line joining the umbilicus with the center of the pubis, and a point in the left interscapular region, and approximately at the level of the spinous process of the seventh thoracic vertebra. Arrighi showed that his leads and the standard limb leads give the same value for the vertical component of the cardiac vector. He advanced cogent arguments in support of his contention that his leads permit an accurate estimate of the sagittal component of this vector. Our only criticism of his approach to the problem is that it involves the taking of three extra leads when only one should be required.

The fact remains that no method of determining the spatial electrical axis of the heart has been very extensively used either by him who originated it or by anyone else. One reason lies in the difficulty of measuring the error involved in any such method that is proposed and of demonstrating that by such means effects produced by rotation of the heart can be recognized with certainty. It seems probable that these difficulties will eventually be overcome.

DESCRIPTION OF AN EXPERIMENT ON A CADAVER

On March 1, 1934, we carried out an experiment on a cadaver for the purpose of ascertaining whether, by converting Einthoven's triangle into a tetrahedron, we could devise a reliable method of computing the position of the spatial electrical axis of the heart. The results of this single experiment, performed so long ago, are reported now chiefly for the purpose of laying the groundwork for future papers dealing with more recent work along the same line, and also because

they have a bearing upon the validity of Einthoven's triangle which has been the subject of a good deal of discussion.

The cadaver used was that of a man who had died more than a week before of carcinoma of the face complicated by pneumonia. During the interim the body had lain in the morgue in the supine posture, and it was suspected that, in addition to pronounced post-mortem changes, there had been considerable gravitation of fluid into the more dorsal tissues. The electrodes used to generate an electric field in the trunk consisted of two brass rods (25 cm. long) covered with rubber except at the sharpened tips. They were fixed in a wooden frame which kept them parallel and 5 cm. apart. This frame permitted the rods to be moved endwise, so that when they were thrust through the precordium, the depth of the tip of each was independently adjustable. After they were in place a potential difference of approximately 18 volts was rhythmically impressed upon these electrodes by means of a rotating contact breaker. Small copper disks with central binding posts sewn beneath the skin with the binding post projecting through it served as electrodes for the leads employed. One was placed on the lateral surface of each arm at the level of the insertion of the deltoid muscle and another on the inner aspect of the left knee joint. The fourth was placed on the back just to the left of the midline and at the level of the spinous process of the seventh thoracic vertebra.

The leads taken were standard Leads I, II, and III and leads from a central terminal to each of the four electrodes. These last leads will be referred to as Leads V_R , V_L , V_F , and V_B , respectively. On most occasions when these unipolar leads were taken, resistances of 10,000 ohms were used to connect the central terminal to the limb and back electrodes. Once 5,000 ohm resistances were employed. In a few instances the resistance between the central terminal and the back electrode was increased to 15,000 or 20,000 ohms or was removed. The effects of shifting the arm electrodes to the anteromedial margin of the shoulder joints and the leg electrode to a point just above the pubis were also investigated.

During the course of the experiment the electrodes used to generate the field occupied four different positions as follows:

Position A. Both electrodes in the third intercostal space. The minus electrode was close to the right and the plus electrode close to the left border of the sternum. The tip of the former was 5.7 cm. and that of the latter 8.8 cm. beneath the skin. The line joining these made, therefore, an angle of 32 degrees with the frontal plane. Its projection on this plane was parallel to the line of Lead I. The tips of the electrodes were 5.9 cm. apart, and their mean distance from the front of the chest was 7.25 centimeters.

Position B. Same as Position A except that the depth of the minus electrode was 5 cm. and that of the plus electrode 10 centimeters. The line joining their tips made an angle of 45 degrees with the frontal plane. This line was 7.1 cm. long and the depth of its midpoint was 7.5 centimeters.

Position C. The minus electrode was in the fourth intercostal space and the plus electrode in the third. Both were close to the left edge of the sternum. The tip of the first was 5.5 cm. and that of the second 10.7 cm. beneath the skin.

The line joining these tips was 7.2 cm. long and the depth of its midpoint was 8.1 centimeters. The angle made by it with the frontal plane was 46 degrees. Its projection on this plane was not quite perpendicular to the line of Lead I.

Position D. Same as Position C except that the tip of the minus electrode was 5.5 cm. and that of the plus electrode 15 cm. beneath the skin. The line joining the uninsulated tips made an angle of 62 degrees with the frontal plane. It was 10.7 cm. long and its midpoint was at a depth of 10.25 centimeters. The diameter of the chest from front to back was about 21 cm. so that the plus electrode was not more than 6 cm. from its posterior surface.

The measurements of the deflections in the various leads are given in Table I. Figures enclosed in parentheses were computed from those given in the other columns. Einthoven's E and his angle α were derived from the deflections in the standard limb leads in the usual way. At the time when the experiment was performed and before the results were known, the true angle α defined by the line joining the points where the input electrodes penetrated the anterior wall of the chest and the direction of Lead I was estimated at 0 degree for Positions A and B at -100 degrees for Positions C and D. It will be noted that the value of this angle computed by Einthoven's method differed from the estimate of the correct value by no more than 4 degrees for Positions A and B and by no more than 14 degrees for Position C. For Position D the difference was about 30 degrees. It was suspected that this large difference might be due to the gravitation of fluid into the more dorsal tissues, for it appeared when the plus electrode was thrust nearly three-fourths of the way through the chest.

The letter (p) following the capital letter which designates the position of the input electrodes in Table I indicates that the leg electrode was just above the pubis; the letters (sp), similarly used, indicate that, in addition, the two arm electrodes were on the anteromedial aspect of the shoulder joints. It will be noted that these changes in the positions of the electrodes had only trivial consequences. At the end of the experiment the distances from the three electrodes to the points where the brass rods penetrated the chest wall were measured. The distances of the right arm, left arm, and leg electrodes from the minus rod were 24, 18.5, and 37 cm., respectively. The distances of the same electrodes from the plus rod were 20.5, 16, and 41.5 cm., respectively. Since the electrodes were in the same position when Tracing 19 was taken as when Tracings 20 and 21 were made, these measurements throw no light upon the differences between Position C and Position D in respect to the magnitudes of the deflections in the limb leads.

Our chief purpose in making these observations was to ascertain whether Lead V_B would make it possible to measure the sagittal component of the electromotive force. Let us assume that the electrical field set up in the trunk by the voltage impressed on the input electrodes was equivalent to that produced by a centric doublet in a homogeneous spherical conductor. We may, then, consider the limb electrodes and the back electrodes the apices of a tetrahedron inscribed in a conducting sphere. If we regard this tetrahedron as equilateral, the distance between the plane defined by the limb leads and the doublet is equal to one-third of the radius of the hypothetical spherical surface. It may be shown

TABLE I

NUMBER OF TRACING	POSITION INPUT ELECTRODES	E	ANGLE ALPHA	I	II	III	V _R	V _L	V _F	V _R	RESISTANCE TO LIMB ELECTRODES	RESISTANCE TO BACK ELECTRODE
1	A	26.0	0	26.0	12.8	-13.0	—	—	—	—	—	—
2	A (p)	26.0	-3	25.8	12.0	-14.0	—	—	—	—	—	—
3	A	25.0	-1	25.0	12.0	-12.8	—	—	—	—	—	—
4	A	24.5	-2	(24.5)	(11.5)	(-13.0)	-11.5	13.0	0.0	—	10,000	—
5	A	24.0	-1	(24.0)	(11.5)	(-12.5)	-12.0	12.0	0.5	—	5,000	—
6	A	23.0	-1	(23.0)	(11.0)	(-12.0)	-11.0	12.0	0.0	—	10,000	—
7	A	23.5	-2	(23.5)	(11.0)	(-12.5)	-13.0	10.5	-2.0	—	10,000	—
8	A	23.0	-3	(23.0)	(10.5)	(-12.5)	-12.0	11.0	-1.5	3.5	10,000	10,000
9	A	23.5	-1	(23.5)	(11.5)	(-12.0)	-12.5	11.0	-1.0	2.5	10,000	15,000
10	B	24.1	-4	(24.0)	(10.5)	(-13.5)	-13.0	11.0	-2.5	4.5	10,000	20,000
11	B	23.8	-3	(23.8)	(10.8)	(-13.0)	-12.8	11.0	-2.0	3.5	10,000	15,000
12	B	23.0	-1	(23.0)	(10.0)	(-13.0)	-12.0	11.0	-2.0	2.5	10,000	20,000
13	B	23.5	-3	24.0	10.5	-13.0	—	—	—	—	10,000	10,000
14	C	36.3	-88	1.5	-30.5	-32.0	—	—	—	—	—	—
15	C	35.9	-87	(2.0)	(-30.0)	(-32.0)	9.5	11.5	-20.5	—	10,000	—
16	C	35.7	-87	(1.8)	(-30.0)	(-31.8)	8.0	9.8	-22.0	4.0	10,000	10,000
17	C	—	—	—	—	—	—	—	—	5.5	10,000	—
18	C (sp)	—	—	—	—	—	—	—	—	4.5	10,000	—
19	C (sp)	37.8	-86	(3.0)	(-31.0)	(-34.0)	8.0	11.0	-23.0	4.0	10,000	10,000
20	D (sp)	35.0	-70	(12.0)	(-22.5)	(-34.5)	-4.5	7.5	-27.0	24.0	10,000	10,000
21	D (sp)	35.5	-70	12.0	-23.0	-35.0	—	—	—	—	—	—

that if E is the manifest magnitude of the component of the doublet that is parallel to the frontal plane, and if β is the angle between this plane and the axis of the doublet, the deflection in Lead V_B should be $\frac{1}{4}\sqrt{6} E$ multiplied by tangent β . We are here supposing that the resistances connecting the central terminal to the four electrodes are equal.

On the other hand, we may suppose that the plane of the limb leads passes through the center of the spherical surface and, therefore, through the doublet. It may be shown that, in this case, the deflection in Lead V_B should be $\frac{E}{\sqrt{3}}$

multiplied by tangent β , when the central terminal is connected to the limb electrodes only. Before we compare these theoretical values for the deflection in Lead V_B with the values obtained experimentally, it is necessary to point out that the effect of removing the resistance between the terminal and the back electrode, or of making this resistance a multiple of the three equal resistances joining the terminal to the limb electrodes, may be easily computed. If we start with four equal resistances and disconnect the back electrode from the central terminal, without disturbing the other connections, the deflection in Lead V_B should increase by one-third of its original value. If we double the resistance between the back electrode and the terminal instead of removing it, the deflection in Lead V_B should increase one-seventh of its original value; if we increase this resistance by 50 per cent, the size of the deflection in Lead V_B should increase one-eleventh of its original value. The experimental data are not in accord with these predictions, but they are too few and the changes in the size of the deflection concerned are too small to be regarded as decisive. The predictions involve simple algebraic calculations and Kirchhoff's second law, and can, therefore, hardly be at fault.

It will be seen at once that the deflections recorded in Lead V_B are all much smaller than anticipated. Since the two hypotheses with regard to the position of the plane of the three leads with respect to the centric doublet lead to only minor differences in the theoretical size of the deflections in this lead, it will suffice if the values given in Table I, modified in each instance to the extent necessary to eliminate the effect of the resistance inserted between the central terminal and the back electrode, are compared with the value of $\frac{E}{\sqrt{3}}$ tangent β .

The latter is 8.3 for Position A, 13.9 for Position B, 21.1 for Position C, and 38 for Position D. Increasing the magnitude of the sagittal component by altering the relative depth of the two input electrodes always changed the size of the deflection in Lead V_B in the proper direction, but the amount of the change did not bear a constant relation to that predicted. Position B should have yielded a deflection 50 per cent larger than that given by Position A. The actual increase in the size of the deflection was less than 30 per cent. Position D should have given a deflection about twice as large as Position C; it gave a deflection about six times as large.

We attribute the unexpectedly small values for the deflections in Lead V_B obtained in this experiment to the gravitation of fluid into the more dorsal tissues. Whether this opinion is or is not well founded, only additional experiments of a

similar kind can decide. It is not worth while at present to speculate regarding other possibilities. We may also call attention to another result that was unexpected. The rods used as input electrodes were parallel and always 5 cm. apart, and they were always perpendicular to the anterior chest wall. The input voltage was not varied. It is surprising, therefore, that the value of E should be 25 mm. for Positions A and B and about 35 mm. for Positions C and D. Unfortunately, neither the resistance between the input electrodes nor the magnitude of the current flowing between them was measured. A lower resistance, and consequently a larger current, would be expected to increase the value of E , even though the voltage applied remained constant. In the absence of such measurements, we cannot explain satisfactorily why E had one value when the frontal component of the input voltage was parallel to Lead I and another when it was roughly perpendicular to this lead.

SUMMARY

In an experiment on a cadaver, a potential difference was rhythmically impressed upon two small electrodes thrust into the heart or its immediate neighborhood.

The resulting differences in potential between a central terminal and four electrodes connected to it through equal resistances were recorded with the string galvanometer. The four electrodes were on the two arms, the left leg, and the left interscapular region.

By assuming that the electrical field generated in the trunk was equivalent to that of a centric doublet in a homogeneous spherical conductor and that the four electrodes were at the apices of a tetrahedron inscribed in this sphere, the experimental and the theoretical amplitudes of the deflections in the four leads could be compared. In general, it may be said that, with one exception, the deflections in the limb leads had the relative magnitudes expected. The deflections in the lead from the back were much smaller than anticipated. The last result is attributed to circumstances peculiar to the single experiment performed.

APPENDIX

Proposed Method of Finding the Spatial Electrical Axis.—The field of an electric dipole of moment M , located at the center, O , of a homogeneous conducting sphere of radius, R , is given by the equation

$$V_P = M \cos \theta (1/r^2 + 2r/R^3)$$

where V_P is the potential at the point P , r is the length of the line OP , and θ is the angle made by this line with the axis of the dipole. When P is on the surface of the sphere this equation reduces to

$$V_P = A \cos \theta \quad \text{where } A = 3M/R^2.$$

It may be pointed out that $\cos \theta$ of this equation is equal to the sum of the products formed by multiplying each of the direction cosines of the line OP by the corresponding direction cosine of the axis of the dipole.

Let R , L , F , and B be the apices of an equilateral tetrahedron inscribed within the sphere. Take the center of the sphere, O , as origin, and take as X axis the line parallel to RL , as Y axis the line parallel to the perpendicular bisector of RL which passes through F , and as Z axis the line OB . The lines from O to the apices of the tetrahedron will then have the direction cosines listed as follows:

	X AXIS	Y AXIS	Z AXIS
OR	$-\frac{1}{3}\sqrt{6}$	$-\frac{1}{3}\sqrt{2}$	$-\frac{1}{3}$
OL	$\frac{1}{3}\sqrt{6}$	$-\frac{1}{3}\sqrt{2}$	$-\frac{1}{3}$
OF	0	$\frac{2}{3}\sqrt{2}$	$-\frac{1}{3}$
OB	0	0	1

Let the axis of the dipole have the direction cosines a , b , and c . The potentials of the apices of the tetrahedron will then be given by the following equations:

$$\begin{array}{l} V_R = A \\ V_L = A \\ V_F = A \\ V_B = A \end{array} \quad \left(\begin{array}{l} -\frac{1}{3}\sqrt{6} a \\ \frac{1}{3}\sqrt{6} a \\ 0 \\ 0 \end{array} \right) \quad \left(\begin{array}{l} -\frac{1}{3}\sqrt{2} b \\ \frac{1}{3}\sqrt{2} b \\ \frac{2}{3}\sqrt{2} b \\ 0 \end{array} \right) \quad \left(\begin{array}{l} -\frac{1}{3} c \\ -\frac{1}{3} c \\ -\frac{1}{3} c \\ 1 c \end{array} \right)$$

The dipole may be regarded as the vector sum of two components, one of which is parallel to the plane defined by the points R , L , and F , and the other coincident with the line OB . The first of these components will have no effect upon the potential at B , and the second will have identical effects upon the potentials of R , L , and F . We may split A into two parts in the same way and define these two parts by the following equations:

$$\begin{aligned} A_f &= \sqrt{(Aa)^2 + (Ab)^2} \\ A_s &= Ac = V_B \end{aligned}$$

A_f bears the same relation to the first component of the dipole, and A_s the same relation to the second component, that A bears to the dipole itself. A_f may be expressed in terms of Einthoven's E derived from the potential differences between R , L , and F , regarded as the apices of the Einthoven triangle. We have

$$\begin{aligned} E^2 &= (V_L - V_R)^2 + \frac{1}{3}[(V_F - V_R) + (V_F - V_L)]^2 \\ (V_L - V_R) &= \frac{2}{3}\sqrt{6} Aa \\ (V_F - V_R) + (V_F - V_L) &= 2\sqrt{2} Ab \end{aligned}$$

$$\text{Hence } E^2 = \frac{24}{9}[(Aa)^2 + (Ab)^2] = \frac{24}{9}(A_f)^2 \quad \text{or} \quad \frac{1}{3}\sqrt{6} E = A_f$$

Since $A_s = V_B$, we have then

$$A = \sqrt{A_f^2 + A_s^2} = \sqrt{\frac{1}{3}E^2 + V_B^2}$$

The angle made by the axis of the dipole with the plane of RLF may be found by the formula, $\cot \beta = \frac{1}{3}\sqrt{6} E/V_B$.

It will be noted that $V_R + V_L + V_F + V_B = 0$ and if electrodes at the points R , L , F , and B are connected to a central terminal through equal resistances, this terminal will be at zero potential for all values of a , b , and c . The four leads

from the central terminal to the four electrodes will, therefore, record the potentials V_R , V_L , V_F , and V_B .

Let us suppose that the points R , L , and F are the apices of the triangle inscribed in the great circle represented by the intersection of the XY plane with the spherical surface, and that B is the point where the positive half of the Z axis penetrates this surface. The potentials of the four apices of the tetrahedron $RLFB$ will then be given by the equations:

$$V_R = A (-\frac{1}{2}\sqrt{3}a - \frac{1}{2}b)$$

$$V_L = A (\frac{1}{2}\sqrt{3}a - \frac{1}{2}b)$$

$$V_F = Ab$$

$$V_B = Ac$$

Here $V_R + V_L + V_F = 0$, $E/\sqrt{3} = A_t$, and $V_B = A_s = Ac$

$$A^2 = A_t^2 + A_s^2 = \frac{1}{3} E^2 + V_B^2 \text{ and } \cot \beta = (1/\sqrt{3}) (E/V_B).$$

The potential at the apices of the tetrahedron are recorded by leading to the electrodes at its apices from a central terminal connected through equal resistances to the electrodes at R , L , and F , but not to the electrode at B .

Method of Computing the Effect of Varying the Resistance Between the Central Terminal and the Electrode at B.—If the potentials of the four electrodes at R , L , F , and B are V_R , V_L , V_F , and V_B , respectively, and the potential of the central terminal is V , we have for equal resistances, remembering that the sum of the currents meeting at a point is zero (Kirchhoff's second law).

$$(V_R - V) + (V_L - V) + (V_F - V) + (V_B - V) = 0$$

$$V = \frac{1}{4} (V_R + V_L + V_F + V_B)$$

$$(a) \quad V_B - V = \frac{3}{4} V_B - \frac{1}{4} (V_R + V_L + V_F)$$

When the resistance between the central terminal and the electrode at B is twice as large as the others we have

$$(V_R - V) + (V_L - V) + (V_F - V) + \frac{1}{2} (V_B - V) = 0$$

$$V_R + V_L + V_F + \frac{1}{2} V_B = \frac{7}{2} V$$

$$(b) \quad V_B - V = \frac{6}{7} V_B - \frac{2}{7} (V_R + V_L + V_F)$$

$$\frac{4}{3} (a) - \frac{7}{6} (b) = V_B - \frac{1}{3} (V_R + V_L + V_F)$$

$$(b) = \frac{8}{7} (a) = \frac{6}{7} [V_B - \frac{1}{3} (V_R + V_L + V_F)]$$

Note that $V_B - \frac{1}{3} (V_R + V_L + V_F)$ is the difference of potential between the central terminal and the electrode at B when the connection between the terminal and this electrode is broken and the other connections are left undisturbed.

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ENDOCARDIAC ELECTROCARDIOGRAM OBTAINED BY HEART CATHETERIZATION IN THE MAN

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IN 1929 Forssmann,¹ after having his median basilic vein exposed by a surgeon, performed upon himself the first cardiac catheterization by introducing a ureteral catheter into the vein. This method has been used subsequently by several authors for various research purposes.

A year later Klein² determined the heart's minute volume in man, after Fick's principle, with venous blood obtained by catheterization of the right auricle. Similar determinations were carried out afterward in normal subjects by other authors.^{3,4,20} Cournand and Ranges⁶ described the technique of cardiac catheterization without exposure of a vein. Other hemodynamic investigations by means of cardiac catheterization have been carried out in pathologic conditions,⁷⁻¹³ in the study of different drugs,^{14,15} in septal defects of the heart,¹⁶ and as a complement of radiologic examination.¹⁷⁻¹⁹

We have not found reports in the available literature of the application of this method to electrocardiographic studies. The endocardiac records which are mentioned in some papers have been obtained in animals by introduction of the electrodes into the veins of the neck or needles into the cardiac cavities through the walls of the heart.²¹⁻²⁴ It is the purpose of this paper to show the different electrocardiographic variations that are revealed by direct unipolar leads recorded within the chambers of the heart by cardiac catheterization.

The electrode placed inside the cardiac cavities functions as an active or exploring electrode and is in contact with the endocardial surface of the heart by means of the intracardiac blood. The term endocardiac electrogram means, therefore, an electrocardiogram obtained by a direct lead from the endocardial surface of the heart.

TECHNIQUE AND MATERIAL

We used a No. 8 ureteral catheter with a silver mandril inside and an electrode of the same metal 3 mm. long and 1.5 mm. wide at the tip. The catheter was introduced through the basilic vein up to the cardiac cavities, the position of the electrode being ascertained by radioscopic or x-ray examination.

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To obtain the electrocardiograms we used a central terminal and connected the electrode of the left leg to the catheter. The records were made on Lead II. In this way the endocardiac electrode acted as an active exploring electrode. Connections were so arranged that when the exploring electrode became relatively positive, a positive deviation resulted in the tracing.

This procedure was used in twenty-three individuals (twelve normal subjects, two patients with left and one with right bundle branch block, two with ventricular extrasystoles, one with auricular fibrillation, one with auricular asynchronism and myocardial infarct, three with auriculoventricular dissociation, and one with Wolff-Parkinson-White syndrome). In some of these patients the procedure was repeated.

Standardization was 1 cm. per millivolt in auricular records and 2 mm. per millivolt in ventricular records.

AURICULAR ELECTROENDOCARDIOGRAM (ENDOCARDIAC P WAVE)

The electrocardiographic record of the auricular activity obtained by introduction of the electrode into the right atrial cavity is, in general, uniform. The auricular complex (P wave) begins sometimes with a slight downward deviation, 0.5 mm. or less in amplitude. An upward deviation of variable amplitude (from 2 to 12 mm.) follows, and, after this deflection, a new downstroke (4 to 20 mm.) is registered. From the ascending branch of the last negative deviation, generally at a point 2.5 to 7 mm. below the isoelectric level but occasionally from a point above this level, an upward wave begins which develops more slowly and is the beginning of the slow phase of the auricular complex. This wave rises 3 to 5 mm. above the isoelectric level and ends on a base line from which the ventricular complex begins. The duration of the auricular complex, thus considered, is 0.12 to 0.14 second.

The auricular complex consists, thus, of two parts: an initial rapid deflection, which is at first negative, then positive, then negative or first positive, then negative, and a slow part, which is generally negative in the first and positive in the second phase (Fig. 1). In order to facilitate the interpretation of these various deviations, we shall apply to them the letters used by Brown²⁵ in the esophageal electrocardiogram, with the exception of those used for the initial wave. Consequently S is assigned to the first negative deviation of the "endocardiac P wave"; *e* to the second positive deflection, *i* to the third negative deviation, *o* to the ascending branch of this wave, and *u* its final slow portion.

Comment.—

S Wave: We consider the first negative deflection S as the expression of the initial electric activity of the heart, activation of the sinoauricular node. It precedes the rapid auricular complex proper by approximately 0.02 second. This interpretation is supported by the fact that the nearer the catheter approaches the junction of the superior vena cava and the right auricle, a region close to the sinoauricular node, the larger and more distinct this wave becomes in successive records. The position of the catheter in relation to the sinoauricular node has been ascertained by x-ray examination. Another argument in favor

of our interpretation of the S wave is its agreement with Brown's interpretation²⁵ of the esophageal electrocardiogram and with the experiments of Wedd and Stroud²⁶ and of Eyster and Meek²⁷ referred to in Brown's paper. Brown has shown that when the esophageal catheter reaches the region near the left auricle, the activity of the sinoauricular node appears evident as a small negative wave (*s n*) which begins 0.011 to 0.018 second before the auricular complex *sensu stricto*.^{*} We have also observed this small negative S wave in esophageal electrocardiograms. Rijlant²⁸ has also succeeded in recording the sinus activity in man and in some mammals with a cathode oscillograph.

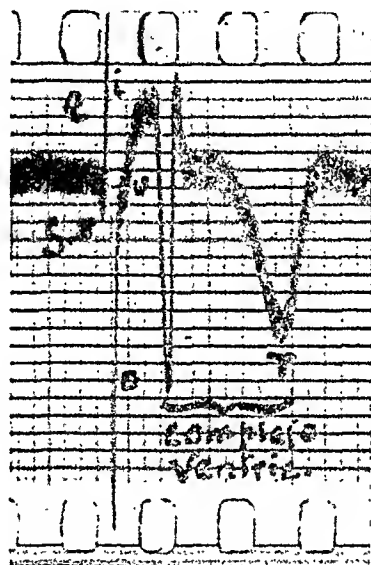
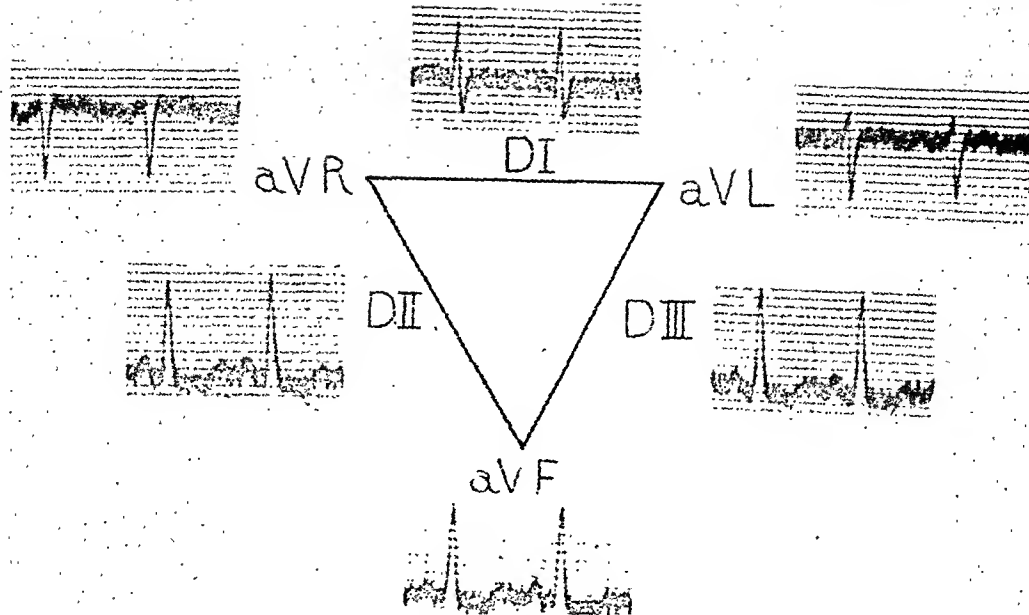


Fig. 1.—Endocardiac electrogram. Amplified tracing obtained with the electrode placed inside the right auricle. The auricular complex composed of S, c, i, o, and u waves and followed by its corresponding ventricular complex can be observed.

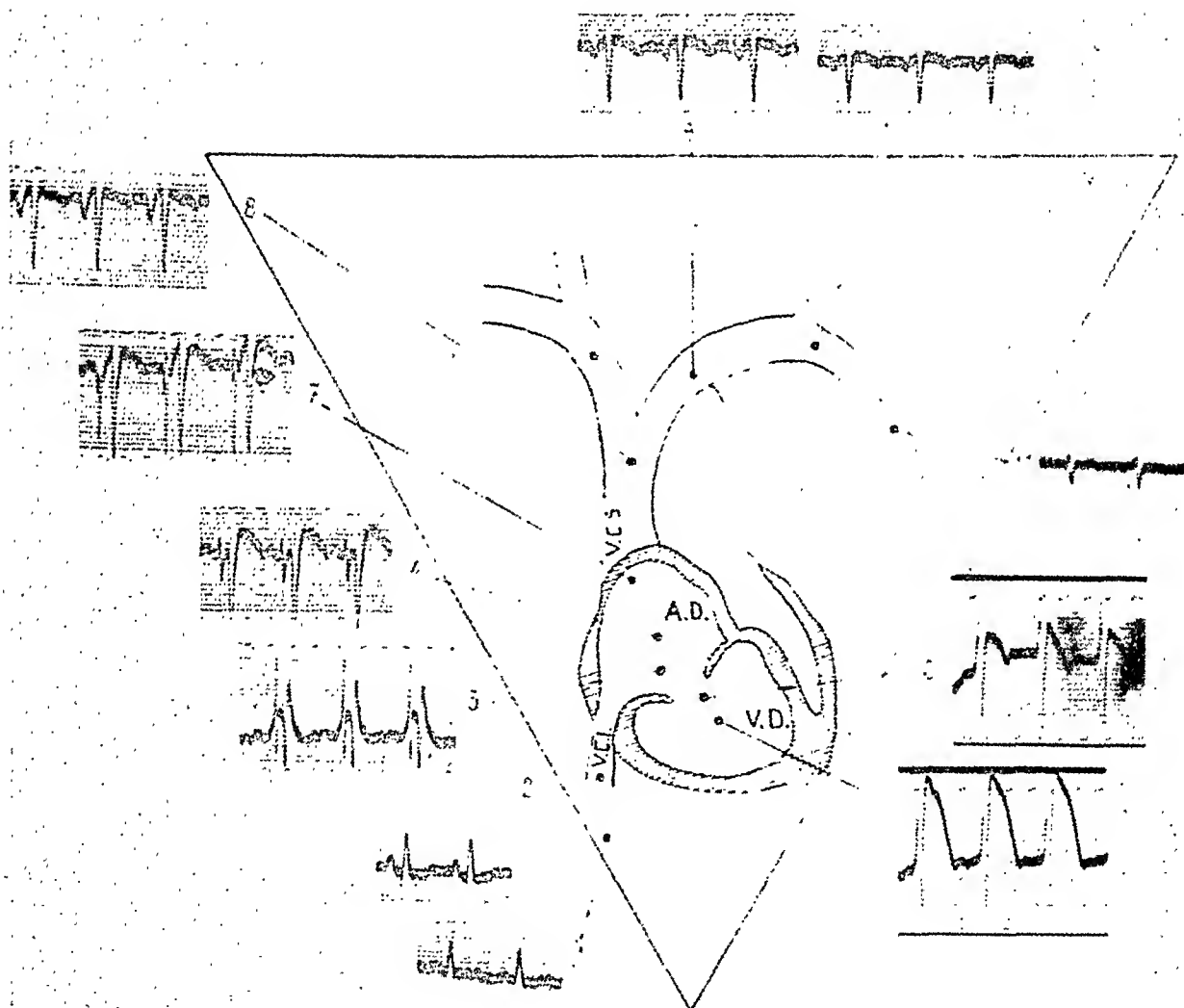
It is possible to explain the negativity of this S wave by the position of the electrode with relation to the sinus. Either the negativity of the endocardiac surface and of the auricular cavity close to it could be registered by the auricular electrode as a negative deflection or the electric potentials, when the sinus is activated, could move farther from the electrode and produce a negative deflection in the electrocardiogram. The S wave would thus represent the process of excitation of the sinoauricular node, inside which a wave of depolarization would also arise. Such a wave with the electrical axis pointed downward would sweep the node and radiate in all directions. It is not possible to trace this activity of the node in the other electrocardiographic leads since it affects these leads slightly.

The c, i, o Group of Waves: The rapid waves of the auricular complex, c, i, o, represent the activation of the atrial walls. The wave of excitation originating

^{*}In referring to this paper we have purposely changed the direction of the waves, since the author registered the electropositivity of the esophageal electrode as a negative deflection and its negativity as a positive deviation, which is the inverse of the technique used in our work.



A.



B.

Fig. 2.—A, Electrocardiogram in Leads I, II, III, aVR, aVL, and aVF in a normal case. Heart in vertical position. B, Endocardiac electrogram of the same case obtained with the electrode placed at various points: right ventricle, right auricle, inferior vena cava, superior vena cava, innominate vein, and left subclavian vein. The catheter was introduced into the left arm. At the level of the superior vena cava and the innominate vein the record is similar to that of aVR; the record obtained in the left subclavian is similar to that obtained in aVL.

in the sinoauricular node spreads through the auricles in all directions and gives rise to a depolarizing wave parallel in direction to the walls of the auricles. In front of this depolarizing wave are the positive potentials of the regions not yet activated and behind it the negative potentials of those muscular fibers just excited.

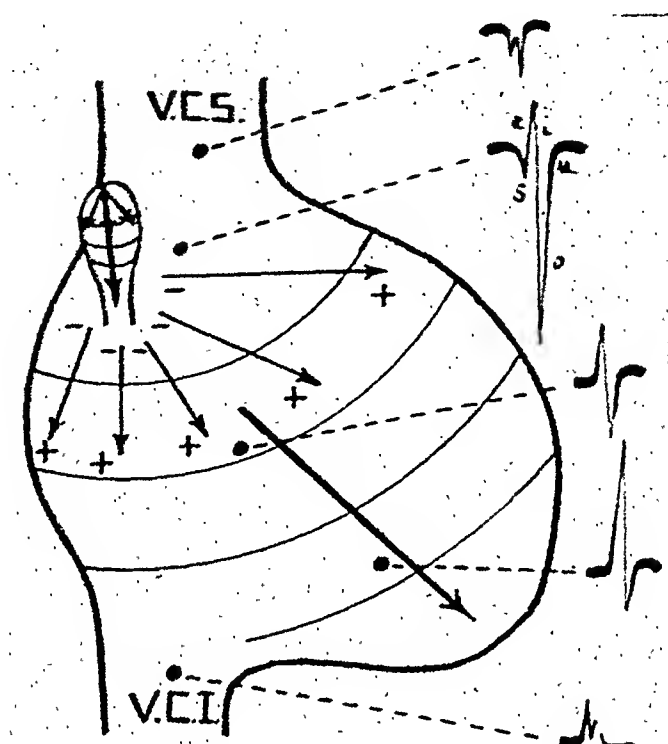


Fig. 3.—An outline of the auricular complex as recorded at different levels.

These electrical potentials influence the endocardiac electrode, the form and amplitude of the waves registered varying according to the situation of the electrode (high, medial, or deep) inside the atrium (Fig. 2). When the endocardiac electrode is placed in the upper portion of the atrium, the excitation waves approaching it produce a small positive *e* deviation, and those waves moving away cause a large negative *i* deviation because of the fact that the portion of the auricular myocardium above the electrode is relatively small and the portion below it is much larger. The reverse happens when the electrode is placed low in the auricular cavity; the depolarizing waves approaching the electrode (big *e* deviation) predominate over those waves moving away (small *i* wave). The potentials which approach and withdraw from the electrode become equilibrated when the electrode is placed in an intermediate position which results in *e* and *i* waves of equal amplitude (Fig. 3).

These endocardiac depolarizing waves are similar to the *e*, *i*, *o* waves of the esophageal electrocardiogram. Brown considers the *i* wave as the "intrinsic" wave, which, according to the conception of Lewis and associates,²⁰ is the deviation representing the activation of the small muscular area in contact with the

electrode. Lewis and associates observed that the intrinsic wave, which indicates the arrival of the excitation wave under the esophageal electrode, is recorded at variable intervals in relation to the P wave of the auricular complex in standard leads.

In the endocardiac electrocardiogram the *i* wave represents also the "intrinsic" wave of auricular activity. Its appearance indicates that the depolarizing wave has reached the electrode and has gone on its way to more distant regions. The *o* deflection shows the activation of the last portions of the auricle and ends when the impulse has spread throughout the auricular wall. At this moment depolarization is complete. The rapid complex *e, i, o* measures from 0.04 to 0.08 second. The auricular endocardiac electrocardiogram, therefore, registers the intrinsic wave which is preceded and followed by extrinsic waves, the latter representing the activation of auricular regions distant from the endocardiac electrode.

The *o-u* segment and *u* wave represent the repolarizing process of the auricles and are similar to the junction point, J, and S-T segment of the ventricular complex. The positive or negative deviations of this segment are due to an acceleration of the repolarizing process caused by tachycardia which generally accompanies the catheterization. The acceleration of cardiac rate in normal conditions can also cause an alteration at the J junction and S-T segment of the ventricular complex. There are cases in which the *o-u* segment is absent and group *e, i, o* ends in a horizontal line which represents the passage of the impulse through the auriculoventricular node.

Ta Wave: In our patients with sinus rhythm, the ventricular complex interfered with the slow waves of the auricular complex. We have been unable, therefore, to differentiate the T wave pointed out by Hering,³⁰ (Ta wave), produced by the auricular activity. However, it was possible in one case of A-V block to record this part of the auricular complex which, as a whole, is similar to the ventricular complex. In this particular case a 2 mm. downstroke which we identify as a Ta wave can be observed immediately after the *u* slow deflection (Figs. 4 and 5). This Ta wave represents the final phase of repolarization of the atria.

The total duration of the auricular activity ($P + Ta$) is 0.60 second. This final wave (Ta wave) of the auricular complex has been demonstrated in man in esophageal electrocardiograms by Boden and Neukirch³¹ and by Sprague and White³² in A-V dissociation and auricular extrasystoles.

In standard and esophageal leads the direction of Ta is opposite to that of the P wave. In most cases with an upward P wave, the Ta wave is directed downward. When P appears inverted, Ta is positive. When the depolarizing and repolarizing waves have different directions, the deflections which represent these phases in the electrocardiogram are concordant, as happens normally in the ventricles (R and T waves, respectively). At the level of the auricles the depolarizing and repolarizing waves have the same direction which results in a discordant inscription in the electrocardiogram: a positive P and negative Ta.

According to Sprague and White³² the interval $P + Ta$ measures 0.34 to 0.42 second and the relation $\frac{P + Ta}{P}$ is 3.7 seconds on the average. Brown²⁵ gives higher figures: 0.405 to 0.503 second and 4.7 seconds, respectively. In our case the interval $P + Ta$ was 0.60 second and the relation $\frac{P + Ta}{P}$ was 5 seconds, as mentioned previously.



Fig. 4.—Amplified auricular electrogram. The auricular complex consists of two phases: a rapid initial part (S, c, i, and o deviations) and a slow final part (Ta wave). The initial negative S deviation indicated by the arrow corresponds to the excitation of the sinoauricular node.

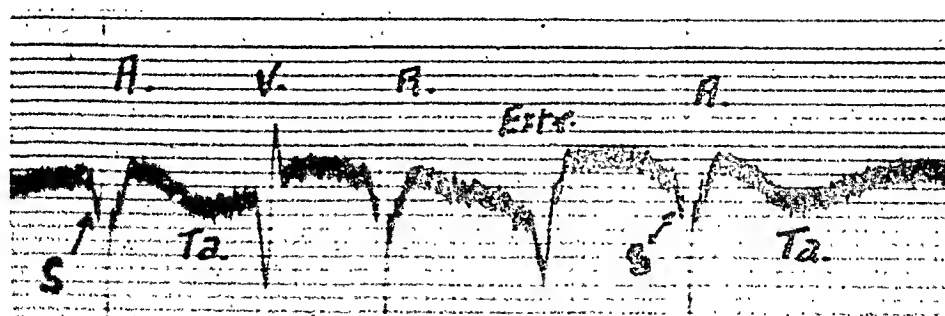
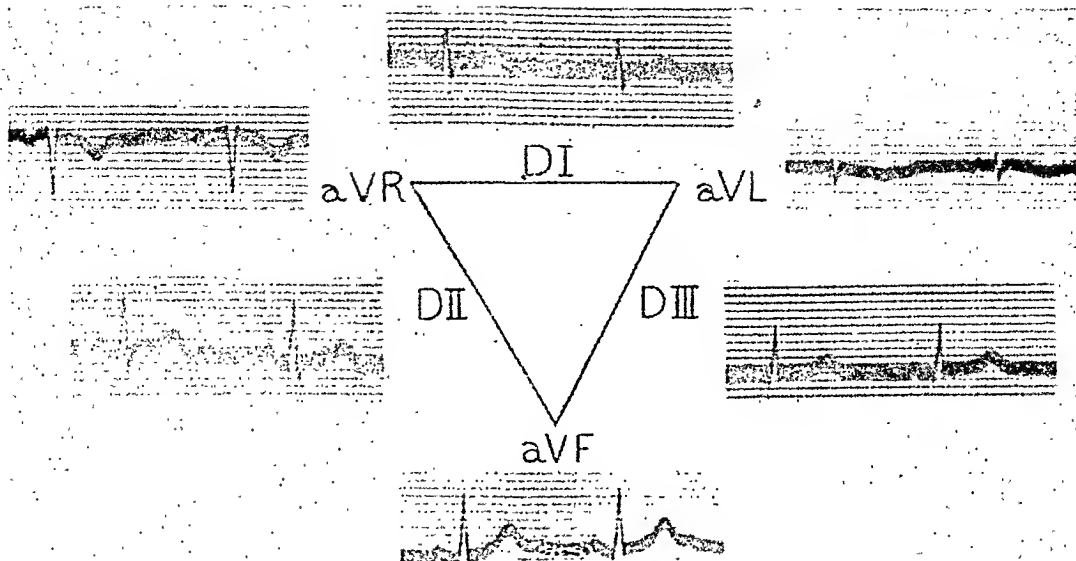
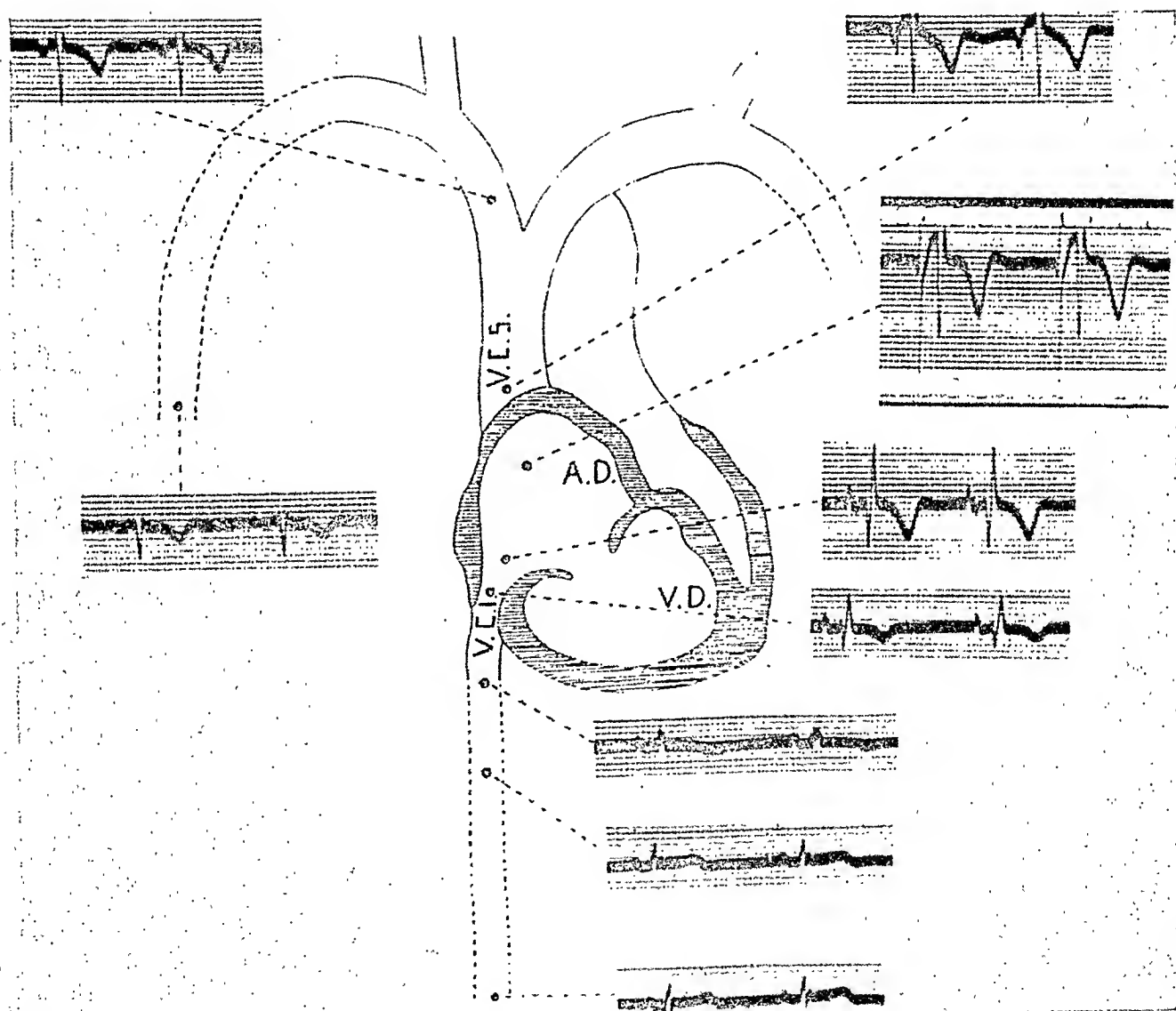


Fig. 5.—Endocardiac electrogram in a case of auriculoventricular dissociation (electrode in the right auricle). It can be observed that auricular activity, A, is independent of ventricular activity, V. Among the last auricular complexes, a ventricular extrasystole appears. The auricular complex shows the characteristics of its sinus origin.

The proper differentiation of the Ta wave is important in diagnosis because, being a negative deflection, it can be traced in standard leads as a depression of the S-T segment and is likely to be regarded as an abnormality of the ventricular complex. The participation of this wave in the QRS group of the ventricular activity is easily explained by the long P-Ta interval.



A.



B.

Fig. 6.—A, Electrocardiogram in Leads I, II, III, aVR, aVL, and aVF. Heart of vertical type. B, Endocardiac and endovascular electrograms. The auricular endocardiac electrogram shows the variations of auricular and ventricular endocardiac potentials according to the position of the electrode, high and low inside the auricle and in relation to the auriculoventricular orifice.

As the electrode descends into the inferior vena cava, the electrogram resembles the aVF lead. Conversely, as the electrode is successively placed into the superior vena cava and in the subclavian and right humeral vein, the electrogram becomes similar to one obtained in aVR.

The P-R segment is frequently observed to have a negative deviation in standard leads. Considering the time of its production in relation to the inscription of the ventricular complex, we feel that it corresponds to the *o-u* segment of the auricular complex rather than to the Ta wave.

As the catheter is progressively withdrawn from the auricular cavity into the superior vena cava, the shape of the auricular complex undergoes a corresponding modification (Figs. 2, B and 6). First the rapid waves (intrinsic and extrinsic waves) disappear; then the auricular complex begins to acquire more and more the appearance of auricular waves in standard leads or in unipolar limb leads, while the *o-u* segment disappears. When the catheter is in the superior vena cava, the P wave usually is negative, of great amplitude, and sharply pointed. In spite of its larger amplitude, it resembles a P wave recorded in aVR leads (Fig. 7, B).

The successive modifications of the auricular complex observed in our studies confirm the findings of Lewis and Rothschild³³ in animals. When their records were taken with the electrode inside the superior or inferior vena cava, a region where these great vessels are surrounded by auricular muscle, they observed disappearance of the intrinsic deflection and the sharp deviations of the auricular endocardiac electrocardiogram.

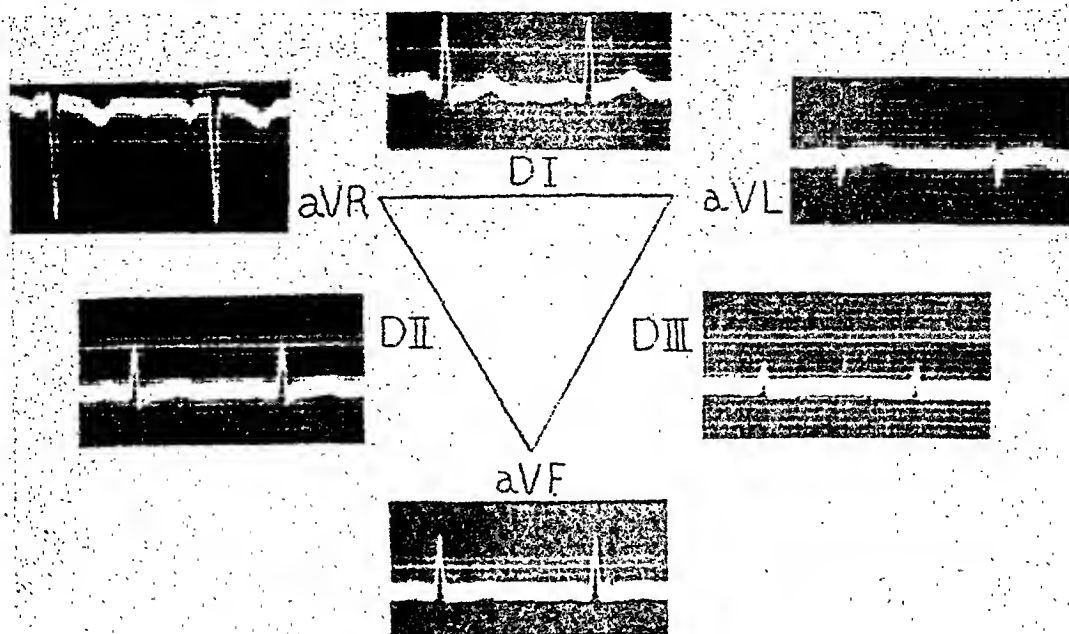
When the records were taken in the innominate vein, the P wave was similar in shape to that of the aVR lead. The same was observed if the electrode was placed in the right subclavian vein or at the level of the right basilic vein. In one case in which the catheter was introduced on the left side, the P wave maintained its negativity in the vein of the left arm although the same P wave in the aVL lead appeared positive (Fig. 7).

By taking successive records from positions between the interior of the heart and the peripheral vessels, variations from an endocardiac P to a P wave characteristic of the standard limb leads can be obtained.

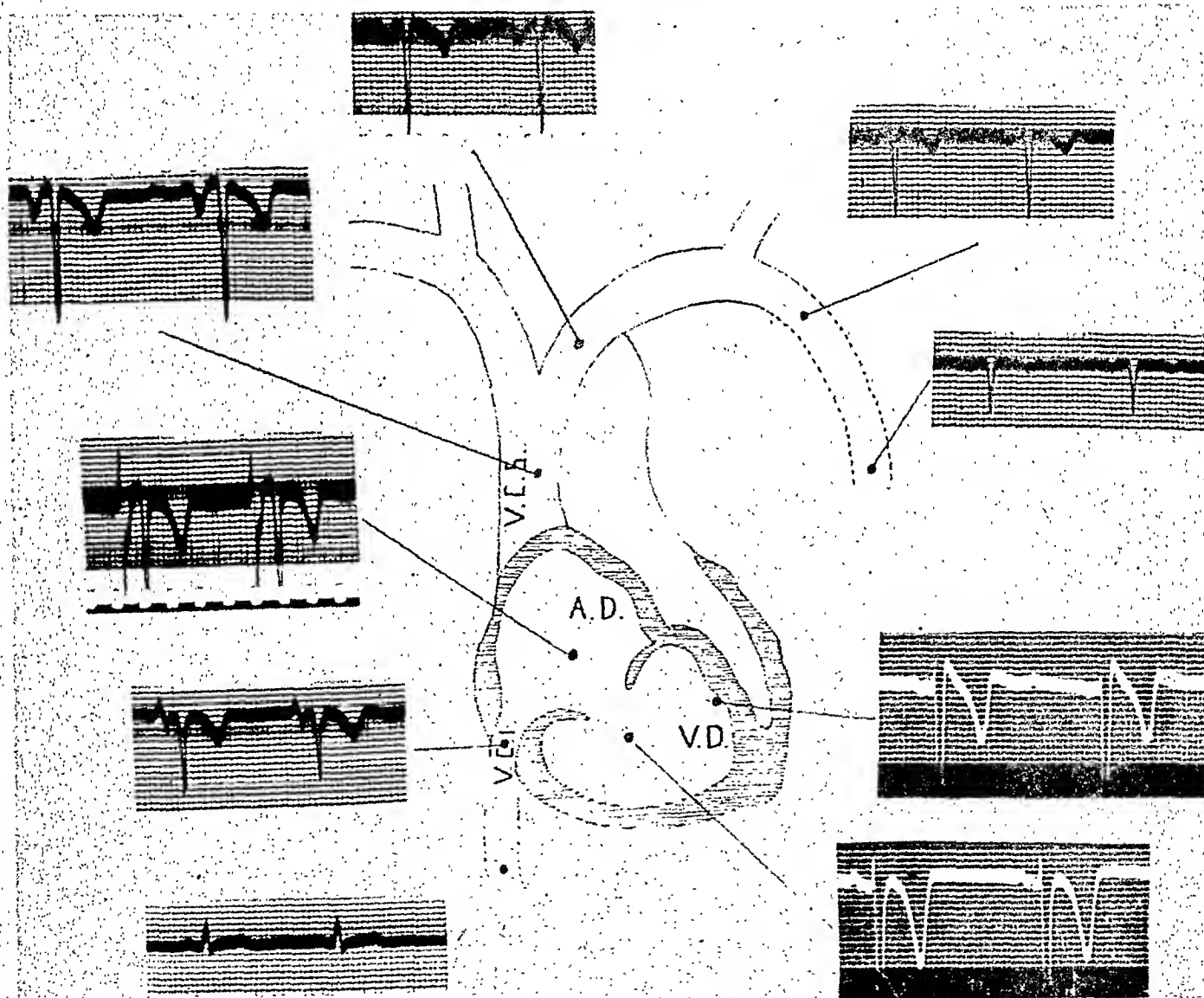
The shape shown by the P wave in standard or limb leads results from the numerous electrical influences that effect the auricular wall and from the difference in the conductivity of the tissues for the potentials produced by auricular contraction. The negativity of P in leads taken from the superior vena cava and from the innominate vein is accounted for by the position of the electrode in relation to the direction of the wave of depolarization of the auricles, which radiates from the sinus node and spreads through the auricular wall away from the exploring electrode. Under these circumstances the auricular electrocardiogram behaves as it does in semidirect leads.

In summary, it can be said that the auricular electroendogram behaves as a direct endocardiac lead and in certain aspects resembles the auricular portion of the esophageal electrocardiogram obtained at the level of the auricles. It consists of a series of initial rapid deflections (S, *e*, *i*, *o* waves) joined to a final slow and negative portion (Ta wave) by a frequently deviated *o-u* segment.

The first negative deflection (S wave), which cannot be registered always is considered to be the result of activation of the sinoauricular node. The rapid deflections (*e*, *i*, *o* waves) constitute the intrinsic and extrinsic waves of the auricular depolarization process, while the final slow wave (Ta) represents the



A.



B.

Fig. 7.—A, Electrocardiogram in Leads I, II, III, aVR, aVL, and aVF in a normal case. B, Electrograms of the same case with the electrode in different situations. Catheter introduced by the left side. At the level of the inferior vena cava the electrogram is similar to aVL. At the level of the superior vena cava and innominate vein it is similar to aVR. At the level of the left humeral vein a negative T wave still persists. At the level of the auricle, the auricular and ventricular complexes are distinctly shown. At the level of the ventricle, the auricular complex is similar to that of the standard leads. The ventricular complex shows the characteristics of the endocardiac ventricular electrogram of type I.

repolarization process. At the level of the superior vena cava the endocardiac auricular electrocardiogram loses its endocardiac characteristics and resembles that obtained in semidirect leads (similar negative P wave but of greater amplitude than the P observed in the aVR lead).

VENTRICULAR ENDOCARDIAC ELECTROGRAM

The ventricular endocardiac electrogram can be recorded from inside either the ventricular or the auricular cavity (types I and II, respectively).

Type I Ventricular Endocardiac Electrogram.—With the electrode placed inside the ventricle, the electrocardiogram shows a rapid deflection followed by a slow one (Figs. 2,B, 7, and 8). The first deflection consists of three phases:

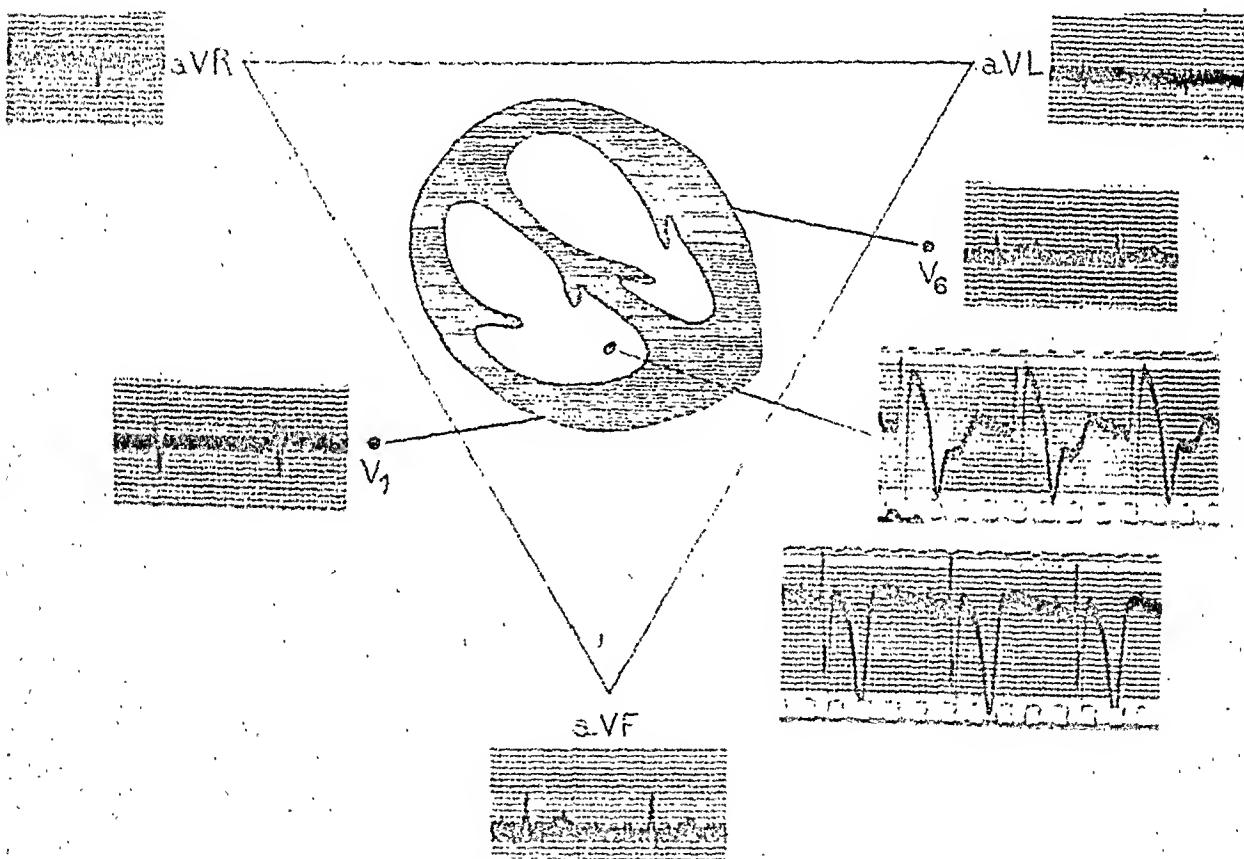


Fig. 8.—Ventricular endocardiac electrogram. A record obtained with the catheter placed in the right ventricle. Variations in the shape of the ventricular complex according to the depth of the catheter can be observed. Precordial electrocardiogram made at Positions 1 and 6 (V_1 and V_6).

an initial upward R wave, a downward S wave, and a third upward inconstant wave, R' . The amplitude of the initial positive stroke varies from 1 to 10 millimeters. The negative stroke has a greater amplitude (from 15 to 20 millimeters). The third positive wave may extend as much as 20 mm. above the isoelectric level. In the same record, however, it may end on the isoelectric line if the position of the catheter inside the ventricle is modified.

The slow wave (T wave) begins generally above the isoelectric level or, less frequently, on the isoelectric line, and describes a curve with an upward and outward convexity. When the slow deflection begins on the isoelectric line, the deviation ends as a large, sharp, and deeply negative wave. When it begins above the isoelectric line, it may go considerably below the isoelectric line or it may stop at this line.

QRS Group: When the catheter is placed in the ventricular cavity, the ventricular complex has, as we have seen, an initial positive deflection (R wave), followed by a negative deflection of great amplitude (S wave). We consider the first deflection (R wave) to be the result of the excitation of the interventricular septum.

According to Ashman and Hull,³⁴ "the interventricular septum is excited on both sides almost simultaneously. However, as the left branch divides immediately below the His bundle the area of depolarization may be at first probably greater and anticipated in the left side of the septum than in the right side." The electrical axis of this depolarizing wave points then from left to right and is not "counterbalanced" by the depolarization of the right side of the septum which has not yet begun.

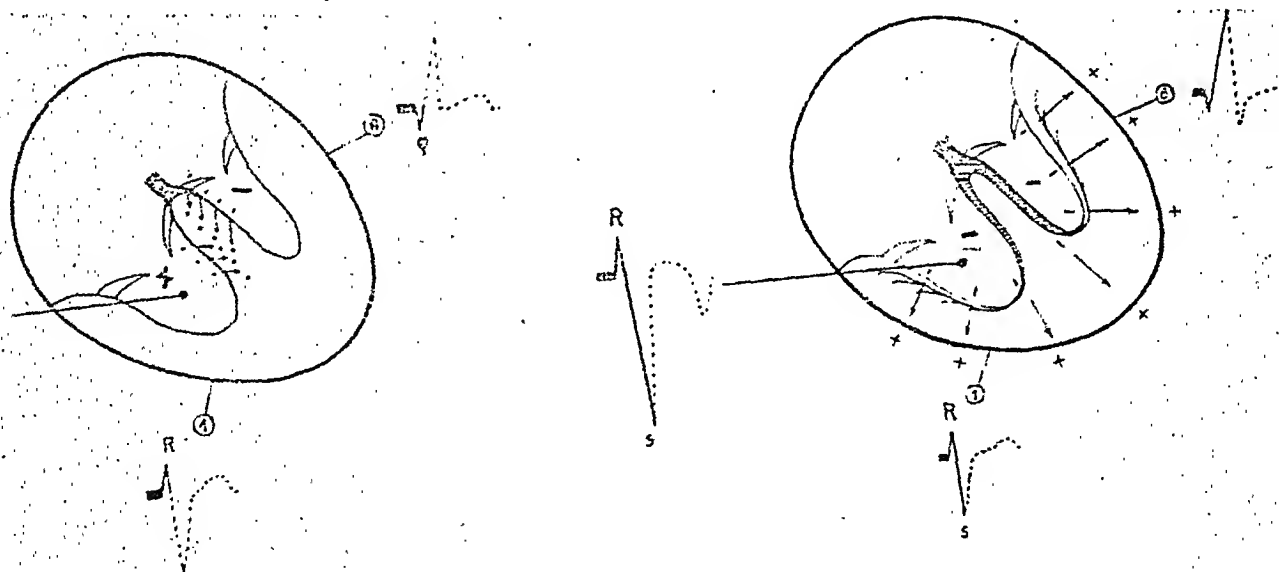


Fig. 9.—An outline of potential variations of the endocardial electrode and of precordial leads made at Positions 1 and 6 at different moments of the process of cardiac excitation (see text).

The waves of excitation of the superior portion of the septum, therefore, travel from left to right; that is, they approach the endocardial electrode and produce the first positive deflection (R wave). In precordial leads this initial activity of the septum is represented by a small initial R wave at Position 1 and by a Q wave at Position 6 (Fig. 9). In fact, when the septum is thus activated, the left ventricular cavity has from the first moment a negative potential and an electrode placed on its surface (Position 6) registers this negativity through the ventricular wall, which is as yet inactivated. A negative deflection, a true septal Q wave, will thus result at points over the surface of the left ventricle.

In its turn the right ventricular cavity will be in the positive field of the excitation wave. Both the endocardiac electrode and an electrode placed over the surface of the right ventricle (Position 1) will record its positivity. Of course a precordial electrode at Position 1 will in its turn be influenced (approximately 0.025 second after) by the activation of the right ventricular wall, the depolarization wave of which, with its positive field displayed forward, advances toward the precordial electrode at points over the surface of the right ventricle, and contributes in this way to the production of the small, initial positive wave.

If this interpretation is correct, the initial positive deflection (R wave) will be absent in an endocardiac electrocardiogram in cases of left branch block because the direction of the depolarization electromotive force of the septum in this case is from right to left. It will be shown later that an R wave does not appear when left bundle branch block is present.

The following negative deflection (S wave) may be considered to represent the negativity of the ventricular cavity at the precise moment that the ventricular complex is registered. Once the septum has been depolarized, the impulse continues to activate the ventricular wall from the endocardiac toward the subpericardiac regions. First the anterior surface of the right ventricle near the interventricular septum is excited, then the excitation reaches the lateral portion of the right and the left ventricles, and finally the base and pulmonary conus of the right ventricle are excited.³⁴

Throughout all this process, due to the direction of the depolarizing electromotive force in the ventricular walls, an electric field is generated which is relatively negative in the endocardiac surface and the ventricular cavity and relatively positive at the crest of the excitation wave as it moves toward the epicardium (Fig. 9).

The endocardiac electrode placed inside the ventricle is thus in a negative field, a circumstance revealed by a large downward deviation (S wave). The excitation waves both from the right and the left ventricles, moving away from the electrode, account for the great amplitude of this deflection. In other words, the electrode registers the negative potential of the right ventricular cavity plus that of the left ventricle transmitted through the interventricular septum which, at the moment, is in a state of complete depolarization. The depolarization of the left ventricle is not completed until a little later because of the greater size and thickness of its wall. The complete depolarization of the ventricular walls coincides with the commencement of the ascending branch of the S wave which sometimes reaches the isoelectric level when depolarization is complete.

If an electrode is placed on the pericardium, Position 1, at the moment the S wave is recorded in a precordial electrocardiogram, it will detect the potentials moving away from it which results in the inscription of a negative deviation (S wave). Conversely, if the electrode is placed at Position 6, it will detect the approaching potentials of the left ventricular wall and consequently an upward positive deflection will be inscribed (R wave).

Endocardiac Ventricular T Wave: This wave is definitely negative, sharp, and deep (Figs. 1, 2, B, 7, and 8), both when recorded with the electrode inside the ventricle or inside the right auricle. It has thus the same direction as the ventricular wave of greatest amplitude. To explain the negativity of this wave it has been assumed that either the repolarization of the ventricular walls begins in the subepicardial region or that the velocity of repolarization is greater in the subepicardial than in the endocardial area.³⁴ The endocardiac electrode is thus placed in the negative field of the wave of regression and a downward deflection (negative T wave) is inscribed. This deflection has great amplitude because it is caused by the negative potentials of both the left and the right ventricles.

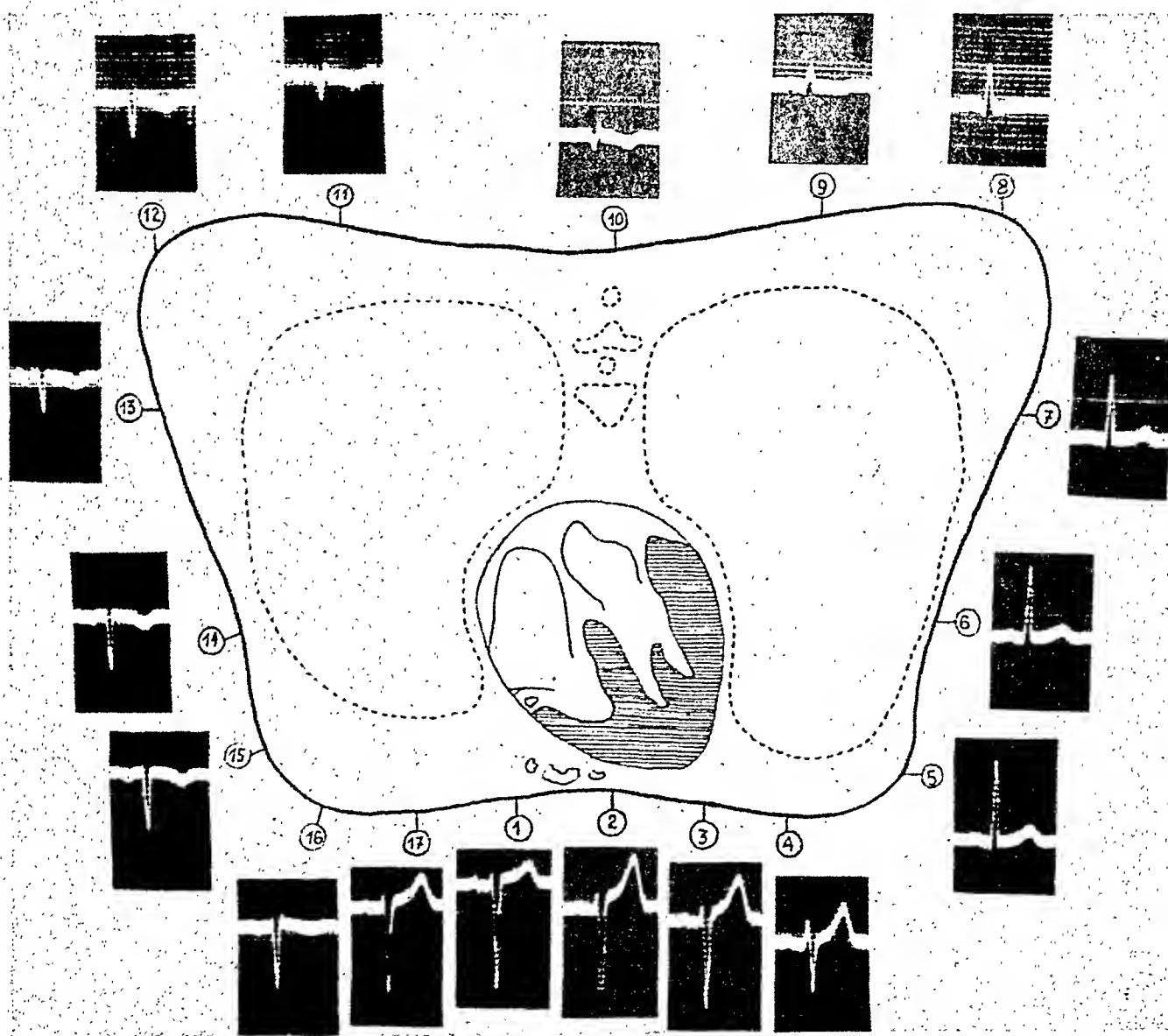


Fig. 10.—Unipolar electrocardiograms obtained from points around the thorax. This tracing belongs to the same subject whose tracings are shown in Fig. 7.

When placed at points on the precordial surface over either the left or the right ventricle, the electrode is in the positive field of the repolarization wave and consequently records an upward deflection (positive T wave).

At precordial Positions 10 to 16, T is recorded as a negative deflection because in this region the ventricular wall has little or no influence, and the electrode is directly influenced by the negativity of the ventricular cavity (Fig. 10).

S-T Segment: The S-T segment of the ventricular electroendocardiogram frequently begins above the isoelectric level. Our tracings indicate that the more deeply the catheter is introduced into the ventricle, that is, the closer the electrode is to the interventricular septum, the greater is its positive deviation. The initial positive deviation of the S-T segment seems to be due, therefore, to the repolarization of the interventricular septum, while the T wave is produced by the repolarization of the free walls of the ventricles. Pardee and Goldenberg³⁵ proved that deviation of the S-T segment was more frequent in cases of infarcts affecting the interventricular septum. Deviation of the S-T segment might also be related to the position of the electrode in the ventricular cavity, its inscription being determined simply by the contact of the electrode against any point of the ventricular wall.

Type II Endocardiac Ventricular Electrogram.—The ventricular electroendocardiogram (Fig. 11) maintains its characteristics even if recorded with the catheter placed inside the right auricle, the only difference in this case being that the initial R wave disappears or is of small amplitude. This peculiarity supports the theory that the initial positive wave of the ventricular electroendocardiogram represents the activation of the septum, since when the catheter is in the auricle it is at a greater distance from the septum and is less influenced by its activation.

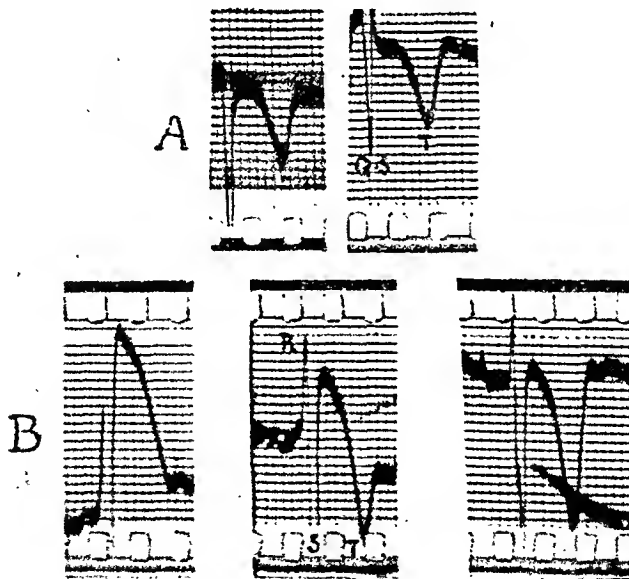


Fig. 11.—Ventricular endocardiac electrograms of types I and II.

When placed in the auricle the electrode detects the negative potentials of the ventricular cavity through the auriculoventricular orifice of the tricuspid valve. Thus, a negative QS deviation and a negative T wave result.

When the catheter is near the A-V opening, it registers a final positive deviation (R'), which disappears when the catheter is withdrawn a little. This R' wave represents the activation of the remaining portions of the ventricles, probably the basal region of the right ventricle and the conus of the pulmonary

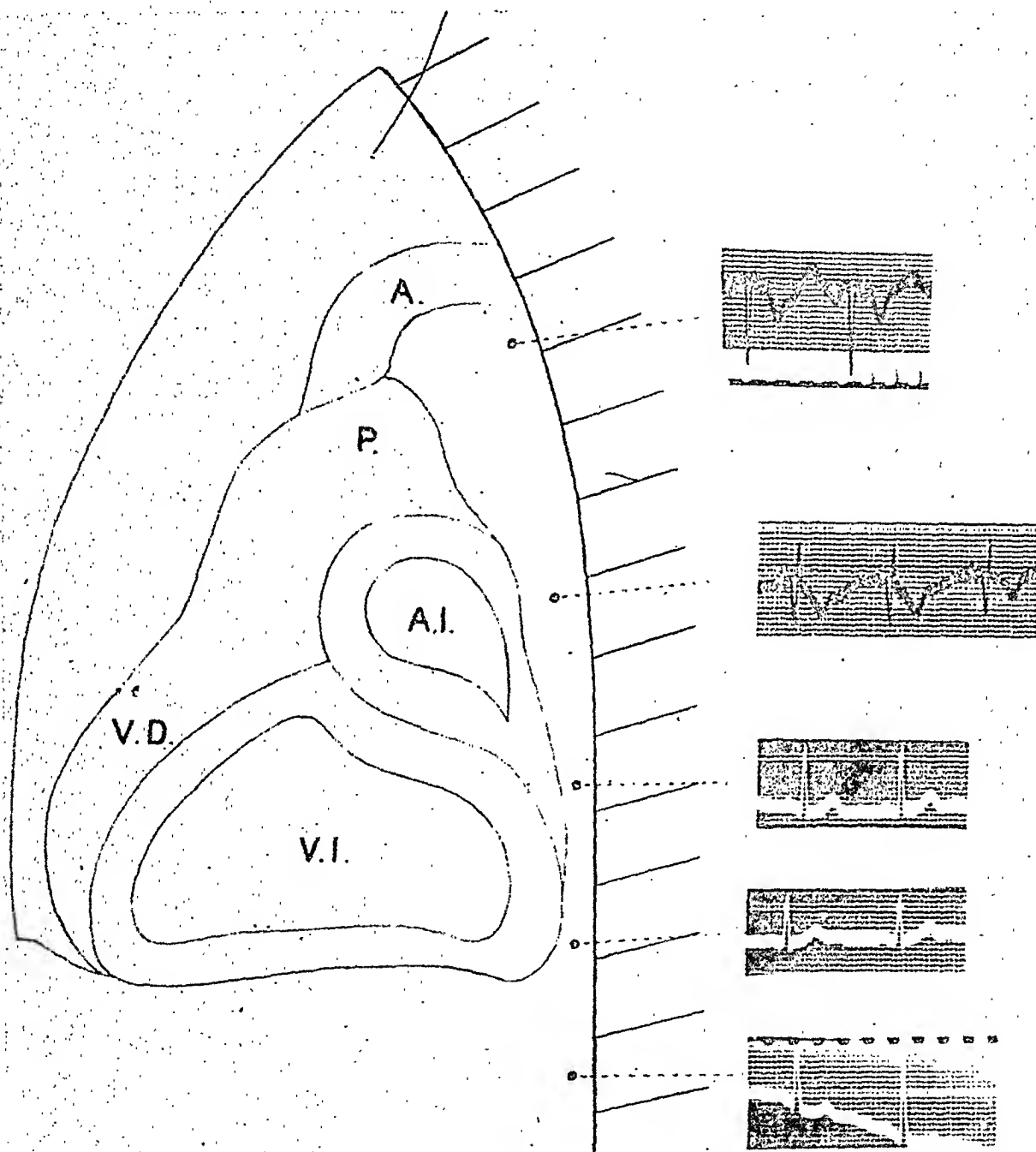


Fig. 12.—Esophageal electrocardiogram at different heights. The esophageal electrocardiogram obtained at the level of the auricle (the second tracing from the top) is similar to the ventricular electrocardiogram obtained with the catheter in the right auricle (type II endocardiac electrogram).

artery. When these zones become excited, the electromotive forces advance toward the electrode placed in the neighborhood and a positive wave will be recorded. This positive deflection has been regarded as the equivalent of the S wave of the precordial electrocardiogram taken at Positions 5 and 6. Such

an interpretation is supported by the observation of a positive final wave in the electroendocardiogram in one case which showed the S wave in tracings taken from Positions 5 and 6. In another case with no S wave in tracings made at Positions 5 and 6, such a deflection was not observed. This type of endocardiac electrocardiogram is similar to the esophageal electrocardiogram recorded at the level of the auricle (Fig. 12).

VENTRICULAR ENDOCARDIAC ELECTROGRAM RECORDED FROM THE VENA CAVA

In records obtained with the electrode placed in the superior vena cava, the ventricular complex has the same characteristics as the ventricular endocardiac electrogram recorded from the auricular cavity except that its amplitude is often less. Its shape also resembles the shape in Lead aVR since an electrode placed in the superior vena cava and an electrode placed on the right arm both have almost the same relation to the valvular openings at the base of the heart. In both cases negativity of the ventricular cavity during the recording of the QRS group of waves is registered. The endovascular electrogram maintains these characteristics (shown in Fig. 6) when taken at the level of the subclavian vein or the veins of the right arm.

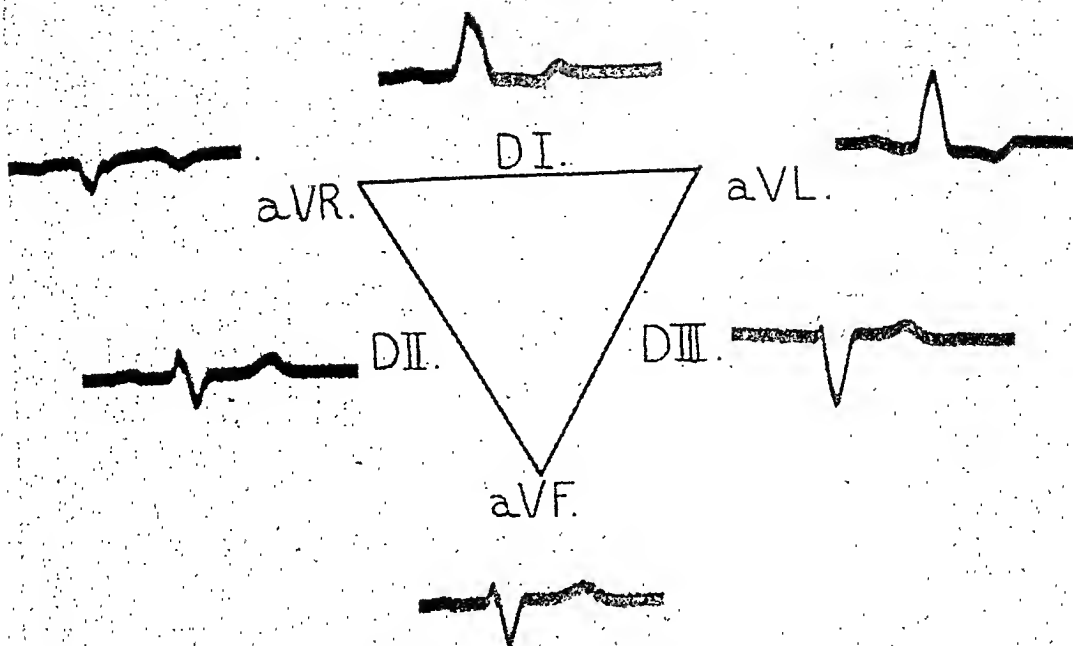
The pattern of the electrogram made with an electrode at the level of the inferior vena cava is similar to the pattern observed in Lead aVF (Figs. 6 and 7). This confirms the observations of Helm and associates³⁶ concerning the distribution of ventricular potentials below the diaphragm. These authors demonstrated that the diaphragmatic type of electrocardiogram is obtained when the variations of potentials are registered from the left leg as well as from the anterior or posterior surface of the abdomen below the diaphragm (upper intestines or duodenum).

VENTRICULAR ELECTROENDOCARDIOGRAM IN LEFT BUNDLE BRANCH BLOCK

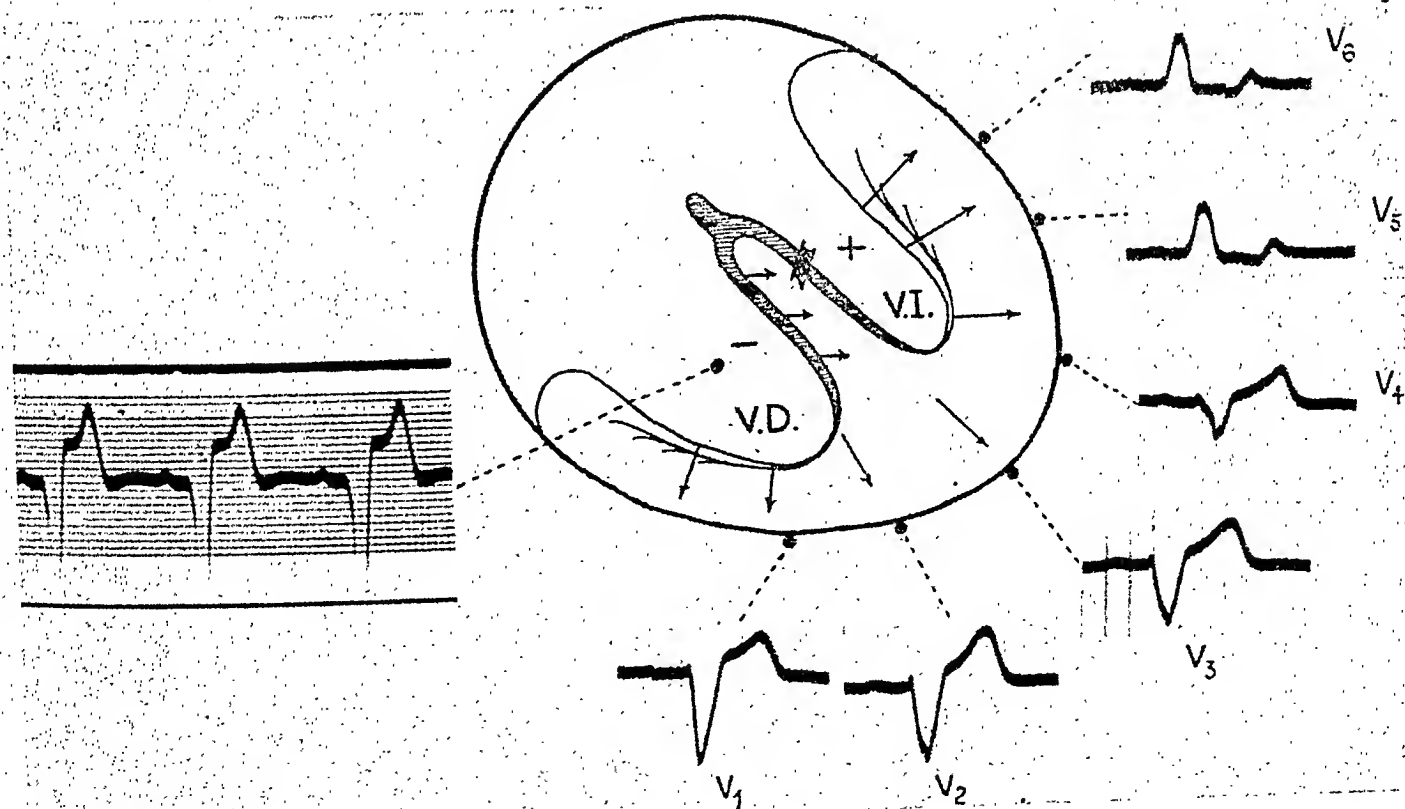
In our cases of left bundle branch block (Fig. 13) the ventricular electrocardiogram recorded with the electrode inside the right ventricle shows no initial positive wave and consists of a simple downward deflection of great amplitude followed by an S-T segment with a positive deviation and a positive T wave.

The shape of this record is similar to the ventricular endocardiac records obtained in animals by Wilson and associates³⁷ after section of the left branch of the bundle of His (Fig. 14). It is also similar to the electroendocardiogram obtained by the same authors from the left ventricular cavity after section of the right branch of the bundle of His (Fig. 17).

The similarity of our tracings to those registered in precordial leads taken at points over the right ventricle is evident (Fig. 13,B).



A.



B.

Fig. 13.—Bundle branch block, common type. A, Electrocardiogram in Leads I, II, and III and in unipolar limb leads. In aVR the ventricular complex is negative. Heart in horizontal position. B, Precordial leads and ventricular endocardiac electrogram of the same case (electrode inside the right ventricle) (see text).

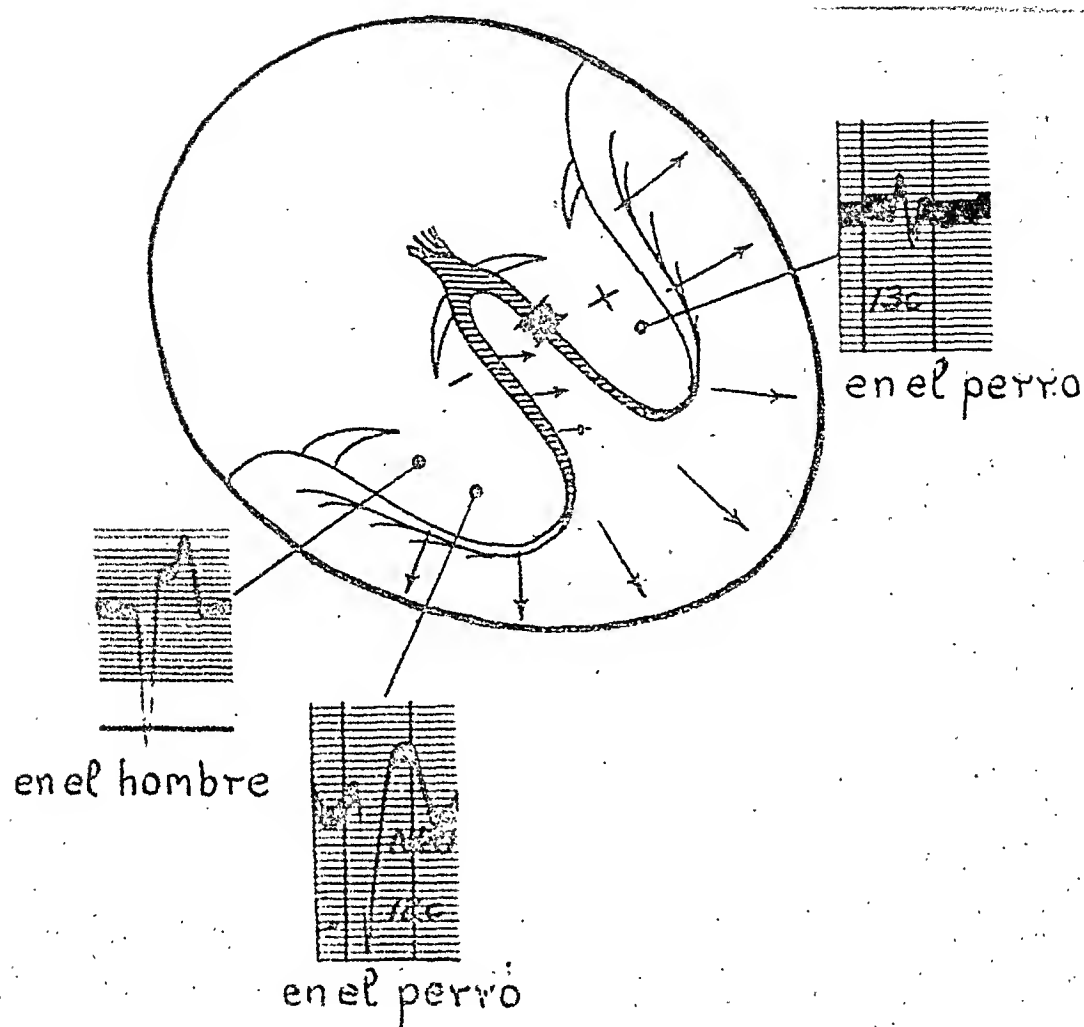


Fig. 14.—Potential variations of the ventricular cavities in left bundle branch block. The right ventricular endocardiac electrogram in man and in one experimental case in the dog (Wilson and associates) show similar variations of potential. The left ventricular endocardiac electrogram in the dog (Wilson and associates) shows an initial positive deviation which represents the abnormal excitation of the interventricular septum, accomplished from right to left.

Interpretation of the Curve.—In left bundle branch block the process of depolarization of the septum does not travel from left to right as is normal conduction, but from right to left. The right ventricular cavity, therefore, remains negative from the beginning to the end of the inscription of the ventricular complex. This explains the change in shape of the ventricular wave to a negative deflection and the absence of the positive initial phase observed in normal cases. Were it possible to put the catheter into the left ventricular cavity of man, as Wilson²⁷ did in dogs, the tracings would show an initial positive phase produced by the spread of the impulse from right to left through the septum.

The peculiar shape of our ventricular electroendocardiogram confirms what has been observed in experimental bundle block. In left bundle branch block something similar to what happens in cases of extrasystoles of the right ventricle

can be observed (Fig. 15): the impulse starts from a focus in the right ventricle and travels to the left ventricle through the interventricular septum. A negative potential is thus produced in the cavity of the right ventricle. We have been able to record this negative potential in one case of left bundle branch block by introducing the electrode into the right auricle.

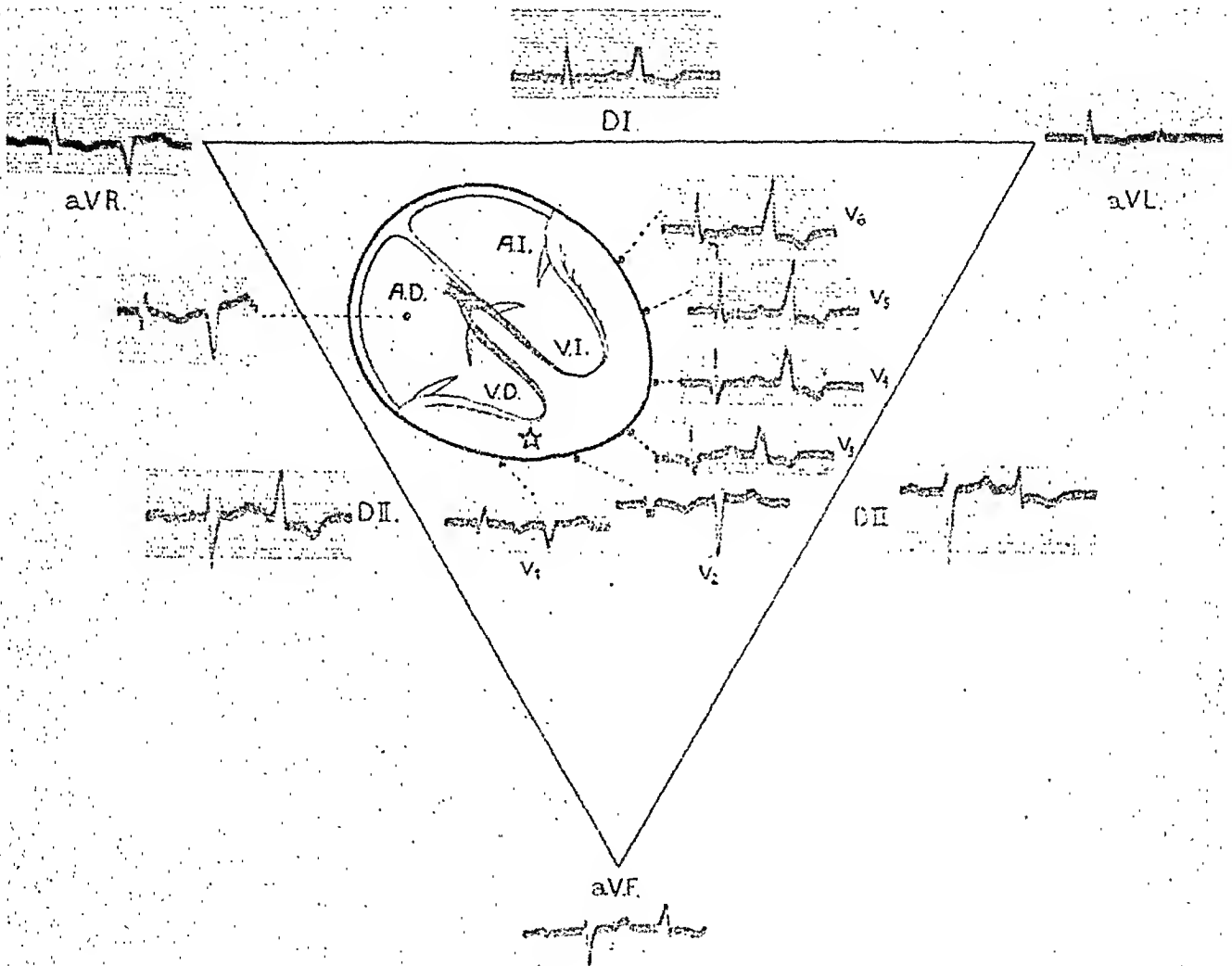
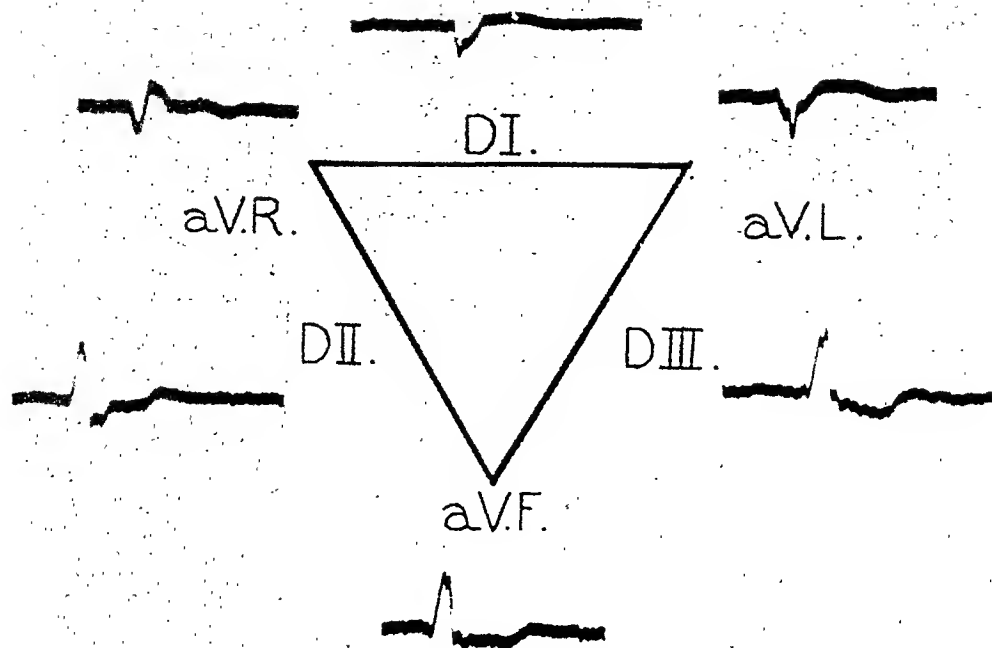


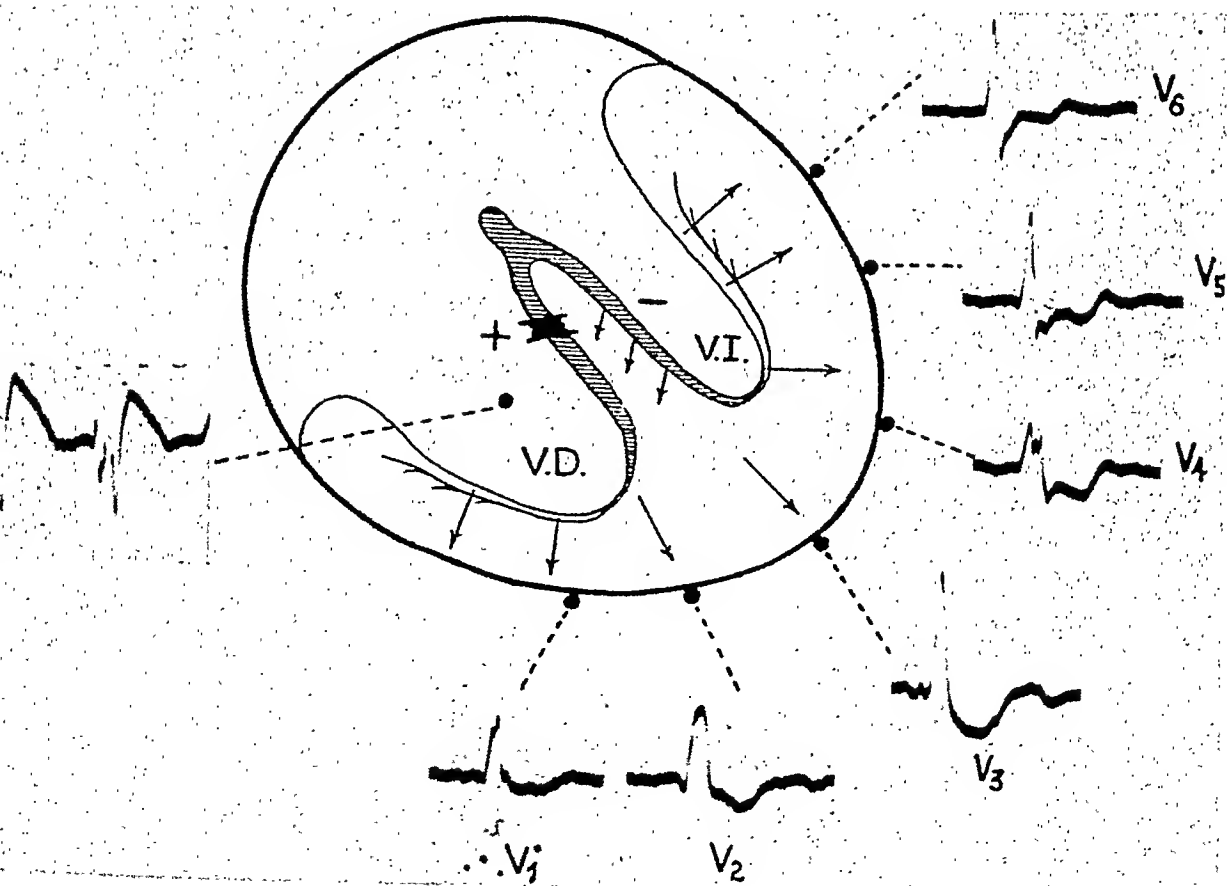
Fig. 15.—Electrocardiogram in standard leads, aVR, aVL, and aVF, and precordial and endocardiac leads in a case of right ventricular extrasystoles. (Electrode in the right auricle.) Heart in semihorizontal position. The extrasystolic complex detected in the auricle has a shape similar to that obtained in aVR and in the leads to the right of the precordial region.

The similarity of the findings in the ventricular endocardiac tracing to the findings in precordial leads made at points to the right and in the right arm lead (aVR) is easy to understand because in both types of tracing the negative potential of the right ventricular cavity is recorded. In precordial leads made from points on the left side and in the left arm lead (aVL), the electrode is placed in the positive field and the direction of the wave of activation is toward the left arm. Consequently a positive deflection results.

In brief, in cases of left bundle branch block, the electroendocardium is similar to the tracings obtained in right ventricular extrasystoles. This fact is



A.



B.

Fig. 16.—Bundle branch block, uncommon type. A, Electrocardiogram in Leads I, II, III and in unipolar limb leads aVR, aVL, and aVF. Semihorizontal type heart. B, Precordial leads and ventricular endocardial electrograms of the same case (electrode in right ventricle). The potential variations of the ventricular cavity are an evidence of the existence of an initial positive phase.

further proof of the accuracy of the modern conception of the origin of left bundle branch block and of ventricular extrasystoles and of the relation of left bundle branch block, particularly, to the electrocardiogram which has been pointed out by one of us (Battro, in collaboration with Braun Menéndez and Orías³⁸) and which is now generally accepted. According to this conception, those tracings which show the characteristics of bundle block and which have a positive deflection in Lead I should be considered to be the result of left bundle branch block.

It is not our purpose to discuss here whether or not there exists in these cases an anatomic lesion localized on the left side of the septum which interrupts the continuity of the bundle of His, a question which has recently been studied by Glomset and associates.³⁹ In any event it can be accepted that tracings which show the characteristics of left bundle branch block, whichever its etiology may be, indicate that in a given case the right ventricle receives the impulse and contracts sooner than the left ventricle.

VENTRICULAR ELECTROENDOCARDIOGRAM IN RIGHT BUNDLE BRANCH BLOCK

In the case of right bundle branch block which we have studied (Fig. 16), the electroendocardiogram taken from the right ventricle shows an upward deflection followed by a downward deflection which is of larger amplitude and notched. The S-T segment shows a positive deviation and is the point of origin of the slow wave corresponding to the period of repolarization (T wave). The T wave ends at the level of the isoelectric line or below it.

The tracing represents the phenomena occurring in the ventricular cavity and the underlying muscle, while the ventricular activity is registered. The right branch being blocked, the supraventricular impulse spreads along the left branch. This results in an activation of the interventricular septum from left to right. In this initial period of activation, the right ventricular cavity will be positive in relation to the left, in accordance with the orientation and direction of the electromotive force existing at the moment. A positive deflection will then appear. In our case this positive deflection has a duration of 0.04 second, a period of time generally considered normal for the travel of the impulse across the interventricular septum.

The only electroendocardiographic tracing published by Wilson and co-workers³⁷ of right bundle branch block in a dog does not show this initial positive deflection, a circumstance which the authors attribute to the initial positivity of the ventricular cavity not coinciding with the beginning of QRS group, as generally happens.

In the standard leads in cases of right bundle branch block, this initial phase of depolarization from left to right of the septum, which should produce a negative wave in Lead I, frequently does not appear because it is neutralized by the electromotive forces of depolarization of the thick wall of the left ventricle. Under these conditions the excitation of the septum can be traced only by placing the electrode close to it.

The left ventricular cavity remains negative during the entire QRS interval, as is shown by the endocardiac record (Fig. 17) published by Wilson and associates.²⁷ The excitation wave reaches the left ventricle first; the right ventricle receives the impulse after some delay. Due to the abnormal course of the excitation wave, potentials which at first move away from and later approach the right ventricle will result. This explains the peculiarities of the QRS complex observed in disorders of this type. Once the impulse has penetrated the septum and reached the fibers of the Purkinje system of the right ventricle, this chamber is rapidly depolarized from the subendocardial to the subepicardial area. During

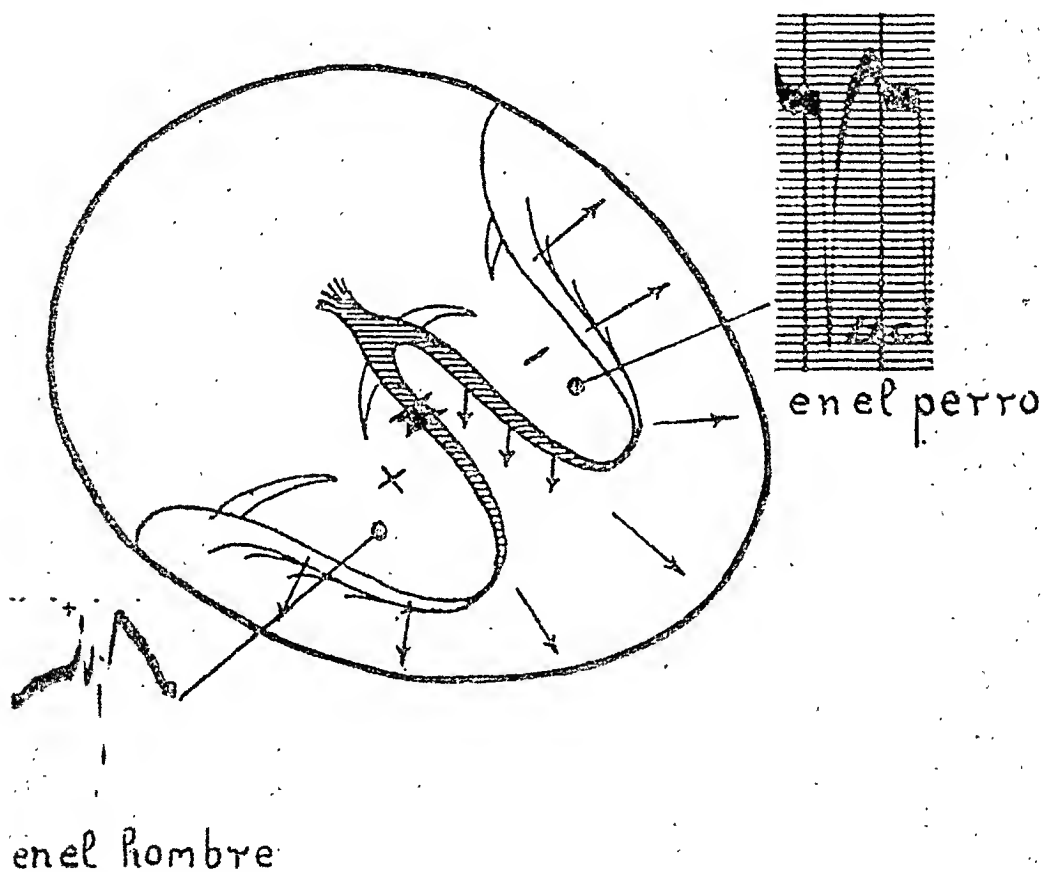


FIG. 17.—Variations of potential of the ventricular cavities in right bundle branch block. The endocardiac electrogram of the right ventricle is from a case of bundle branch block (in man). The electrogram shows the initial positivity of the right ventricle. The endocardiac electrogram of the left ventricle followed experimental bundle block in a dog (Wilson and associates). The ventricular cavity remains negative during all the period of inscription of the rapid ventricular complex.

this last phase, the right ventricular cavity remains negative, a condition evidenced in the electroendocardiogram by a negative deflection.

In left ventricular extrasystoles the developments are somewhat similar to those that occur in right bundle branch block. Because of the abnormal direction of the excitation wave, a positive potential develops in the right ventricular cavity, which we were able to trace in one such case (Fig. 18).

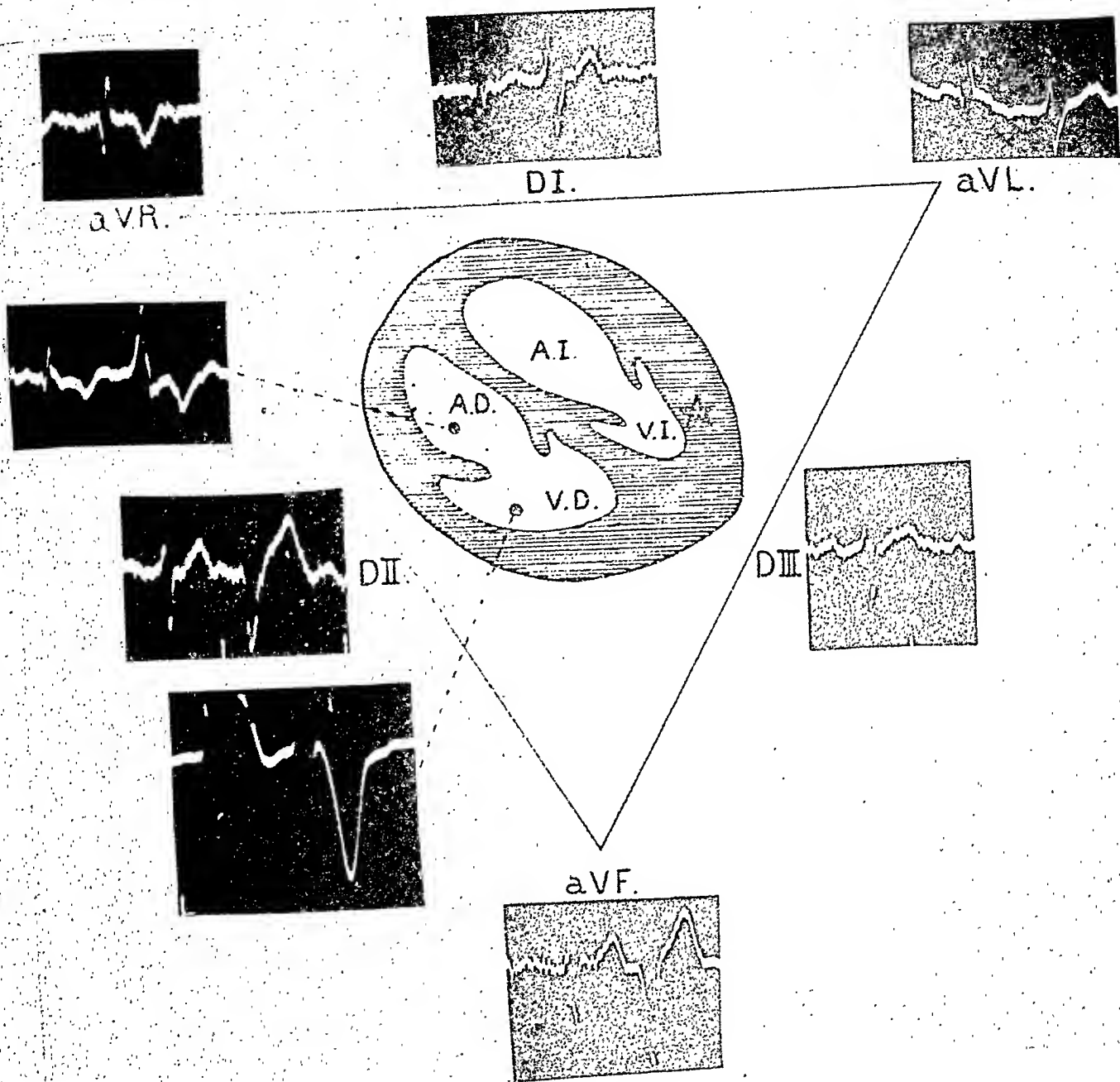


Fig. 18.—Endocardiac electrogram in a case of left ventricular extrasystoles. A record obtained with the electrode placed in the right ventricle and in the right auricle (see text).

ENDOCARDIAC ELECTROCARDIOGRAM IN A CASE OF AURICULAR EXTRASYSTOLES

In one of our cases, the endocardiac tracing made with the electrode placed in the right auricle (Fig. 19) showed a series of extrasystoles of auricular origin. In this tracing with a basic sinus rhythm, each ventricular complex is preceded by its corresponding auricular complex which comprises a positive wave followed by a negative deflection (normal *e*, *i*, *o* waves). When an auricular extrasystole occurs the positive wave disappears and only the negative deflection is present. A suitable explanation is that the extrasystole arises from a focus below the level of the electrode, or from some point relatively far from the electrode, so that the wave of depolarization moves away from it.

The auricular complex which precedes the premature contraction shows almost systematically an increase of voltage just before the extrasystole appears.

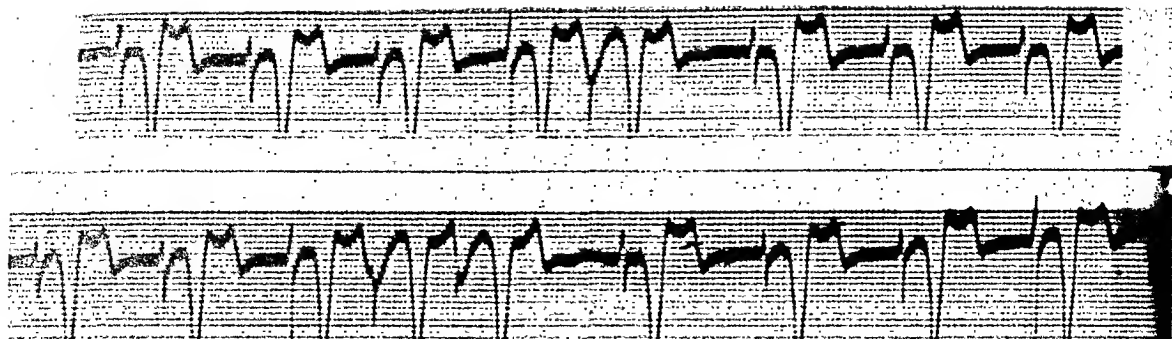


Fig. 19. — Endocardiac electrogram in a case of auricular extrasystoles. (Electrode placed in the right auricle.) The cardiac cycle preceding the extrasystole (Ex. A) shows an auricular complex (P wave) of much greater amplitude. The P wave of the extrasystolic contraction lacks of the positive potential shown by the normal P waves of the rest of the record. This indicates that the focus of origin of the extrasystole is situated in the lower portion of the auricle or below the active electrode.

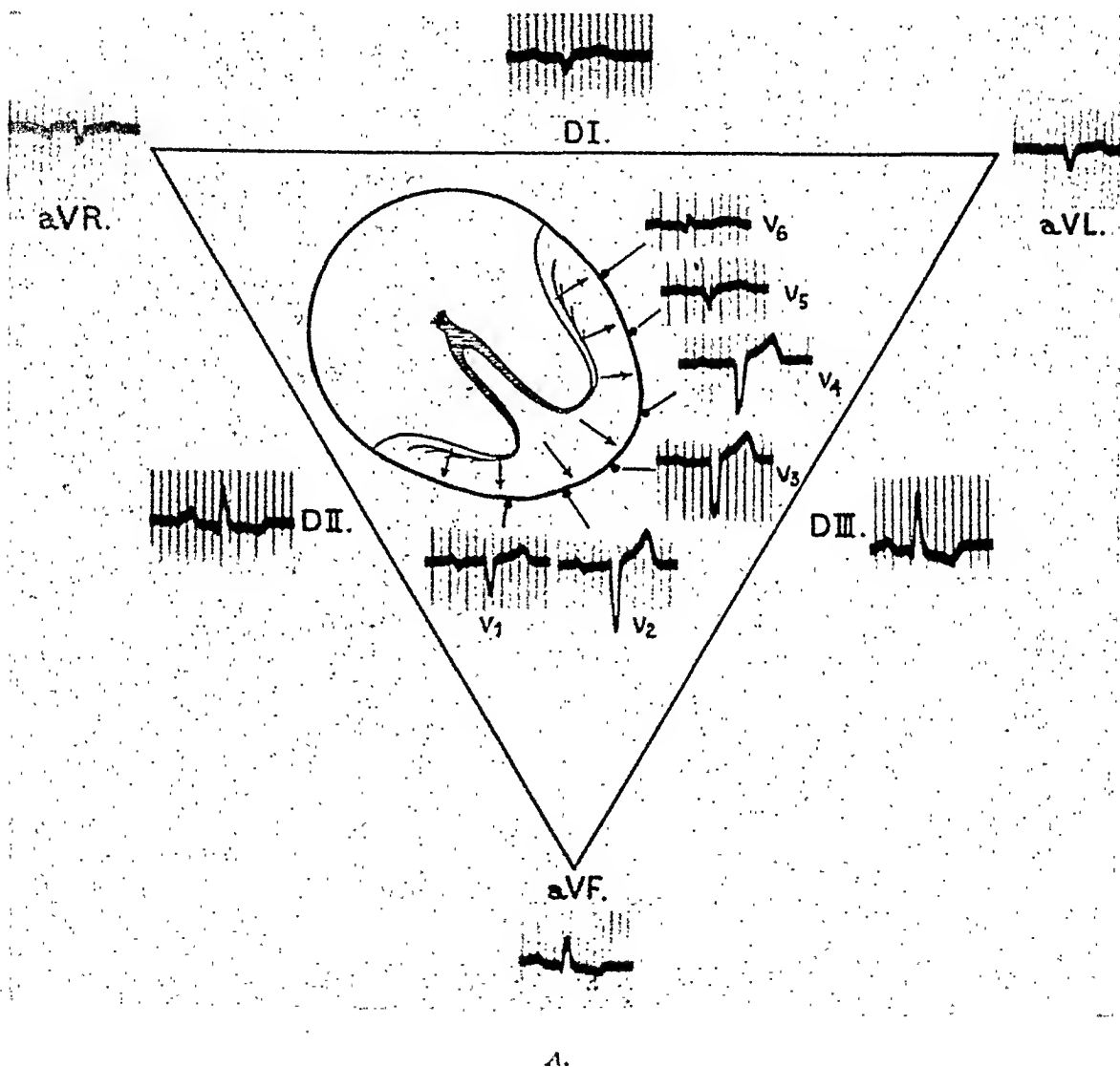


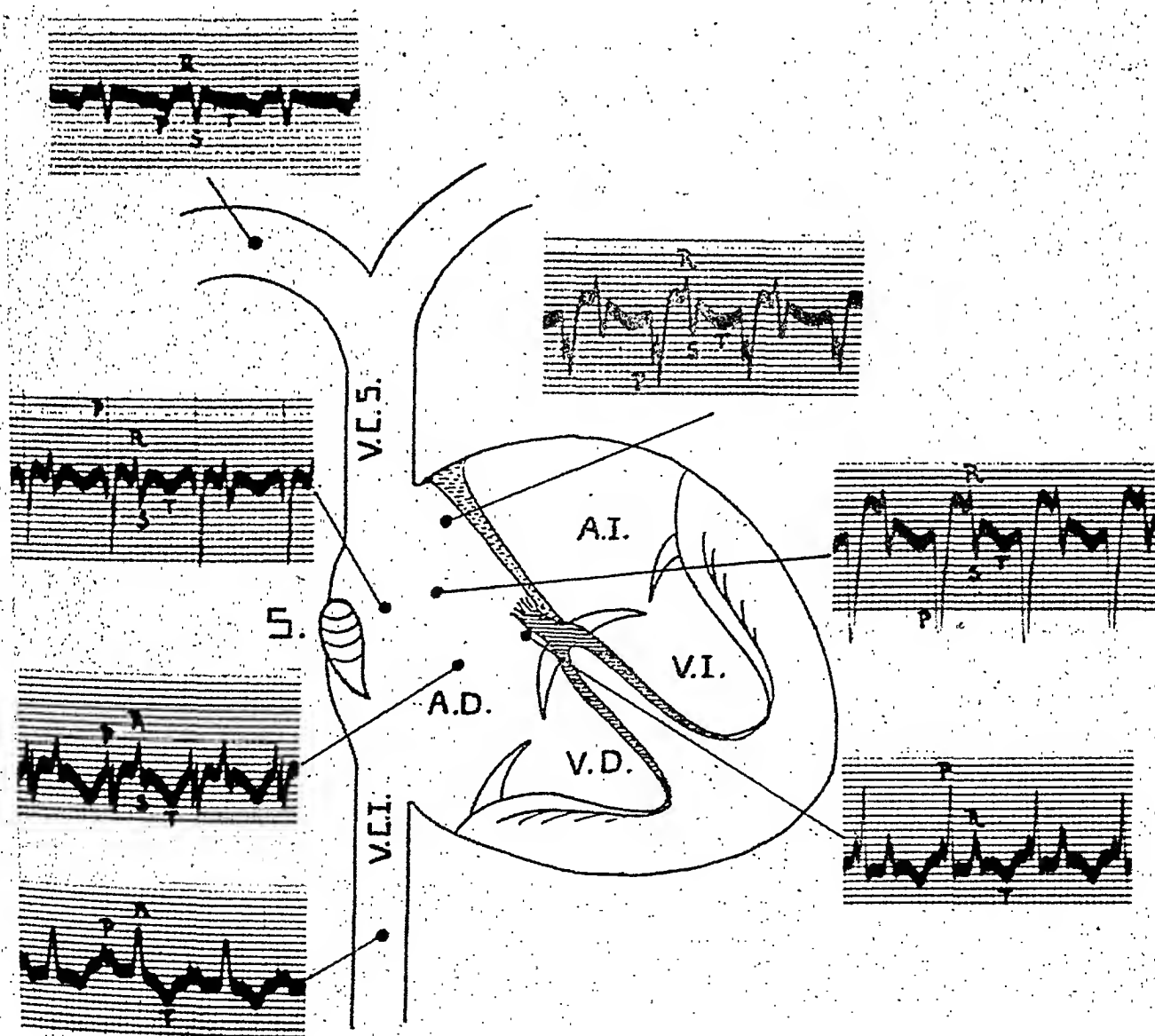
Fig. 20. — A, Electrocardiogram in standard leads, unipolar limb leads, and precordial leads in a case of myocardial infarct and deformation of P wave (notched P wave in Leads II and III). B, Endocardiac electrograms of the same case obtained at different levels of the auricular cavity. The notching of P can be observed in certain positions much more distinctly than in common leads (see text).

ENDOCARDIAC ELECTROCARDIOGRAM IN AURICULAR ASYNCHRONISM

Definite notching of the P wave in standard leads, especially in Lead I and Lead II, with other concomitant abnormalities, such as widening of the base, is regarded as evidence of pathologic alteration of the auricles.

The cause of notching of P has not been settled definitely. Some authors believe that it is due to an abnormal spread of the activation process through the auricles, that the electrical effect of the depolarization process undergone by each auricle is different. According to this theory the notch would simply indicate auricular asynchronism. Notching of the P wave may also indicate occasionally the existence of focal lesions in the auricular wall.

In one of our endocardiac electrograms made with the electrode in the right auricle (Fig. 20), a notched and broadened P wave appeared in Lead II and Lead



B.

Fig. 20 (Cont'd).—For complete legend see opposite page.

III. The shape of the auricular complex varied fundamentally according to the position of the electrode inside the auricle, but in almost all tracings the notching of P is clearly seen. During the depolarization period of the auricle, a downward double deflection is recorded if the electrode is placed in the upper portion of the auricle. With the electrode in a medial position, a W type complex is obtained. When the electrode is placed in the lower portion of the auricle, both deflections are directed upward. We interpret the first peak of P to be the result of activity of the right auricle and the second peak of activity of the left auricle.

The fact that no notching of P has appeared in our normal cases does not confirm Pardee's assumption⁴⁰ that the normal P wave is the algebraic summation of the electric effects produced in each auricle. Were this the case, the endocardiac electrocardiogram would record the activity of both auricles better than any of the ordinary methods.

We are therefore inclined to assume that in normal conditions the depolarizing wave originates in the node and spreads regularly over all the wall of both auricles, as if there were only one cavity. Notching of P is the expression of an alteration in the conduction of the impulse: either one of the auricles receives the impulse after some delay or the depolarization process is accomplished abnormally.

SUMMARY

The electrocardiographic variations registered by endocardiac catheterization in man are described on the basis of twenty-three cases studied.

The tracings show mainly the variations of potential of the heart, detected at the endocardiac surface. Endocardiac leads can be considered to be direct leads. The tracings are endocardiac electrograms.

The auricular endocardiac electrogram (endocardiac P wave) consists normally of a series of rapid deflections (S, *e*, *i*, *o* waves) joined to a final slow deflection (Ta wave) by means of the *o-u* segment. The shape of the auricular electroendogram undergoes modifications according to the position of the electrode inside the auricle.

Rapid deflections represent the process of depolarization of the auricles. Repolarization is represented by the final slow portion, as in the ventricular complex.

The initial negative deflection (S wave) of the auricular complex is regarded as an exponent of the activity of the sino-auricular node.

The endocardiac ventricular electrogram undergoes modifications in shape, depending upon whether the electrode is placed in the right ventricle or right auricle.

The electroendogram obtained from the ventricle (type I) shows an initial positive deviation (R wave) produced by the excitation of the interventricular septum which is followed by a negative deflection of large amplitude (S wave) and a large negative T wave. The waves of depolarization and of repolarization of the ventricular wall (R waves and T waves) have, then, the same direction.

The positive deviation of the S-T segment is greater as the catheter approaches nearer the septum.

The ventricular electroendogram recorded from inside the auricle (type II) traces the negative potentials of the ventricular activity during the spreading of the excitation wave. It begins with a negative deflection (Q or QS wave) followed by a positive deviation, an inconstant element, and ends in a T wave which is usually negative, sharply pointed, and deep. The ventricular complex of this type of tracing is similar to the ventricular complex of the esophageal electrocardiogram obtained when the catheter is at the level of the auricle.

The variations of endocardiac potential in bundle branch block, in one case of auricular extrasystoles, in one case of auricular asynchronism, and in cases of premature contractions of the right and left ventricles are described.

The electrocardiographic curves registered with the catheter placed in the superior and inferior venae cavae and at different sites in the venous system are described.

In bundle branch block of the common type, the endocardiac electrogram taken from inside the ventricle shows the absence of the initial positive (R) wave as a result of the abnormal excitation of the interventricular septum which is accomplished from right to left. The right ventricular cavity remains negative during the inscription of QRS complex. In bundle branch block of the uncommon type the right ventricular cavity is initially positive.

In the cases of bundle branch block which were studied the endocardiac electrogram shows the same characteristics that have been observed in experimental bundle branch block in the dog.

Since our paper was completed, a paper dealing with the same subject has been published by Hecht in the *AMERICAN HEART JOURNAL* 32: 30, 1946. Hecht's conclusions do not coincide with our conclusions in all respects.

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MYOCARDIAL DEPRESSION IN SHOCK

A SURVEY OF CARDIODYNAMIC STUDIES

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APPROXIMATELY sixty years ago, a change in thinking began with respect to the cause of circulatory failure in shock. Previous to that time shock had been attributed to cardiac failure, and its treatment consisted in application of cardiac stimulants or, more precisely, drugs reputed to have such action. With the publication of Groenigen's monograph in 1885 and of Crile's treatise in 1890, the default of the circulation was assigned to the peripheral circulation. Following Henderson's demonstrations^{1,2} that cardiac output and stroke volumes are reduced in shock as in hemorrhage,³ and the more recent demonstrations that reduction in circulatory volume, venous return, and cardiac output precede the fall in arterial pressure,⁴ it came to be accepted that reduction in cardiac output secondary to reduction in venous return was the initiating factor in shock. This constitutes the basic physiology upon which treatment by transfusions of blood, plasma, or substitutes is based. However, military, clinical, and laboratory experiences during World War II are in general agreement that such transfusions are of only temporary benefit in many cases of hemorrhage or shock. In other words, shock, as currently diagnosed, is either reversible or irreversible by adequate transfusions. The hope must not be abandoned that shock may prove to be reversible by other means; but pending such accomplishment we may differentiate between impending or reversible and irreversible states, particularly since evidence is accumulating that generalized cellular damage exists in the latter.

Important as these contributions have been, they do not explain the mechanisms of circulatory failure which redevelop in irreversible states after restoration of normal blood volumes by transfusion. Probably the most plausible and generally accepted hypothesis has been that cardiac output again decreases progressively because venous return fails again. This, however, only leads to another question as to the factors responsible for redevelopment and return of shock. At the beginning of World War II it was the dominant opinion that transfused fluids, including their colloids, continue to be lost from the circulation because capillary endothelium throughout the body becomes more permeable as a result of

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vasoconstriction, hypotension, anoxemia, or toxemia.⁵ In reviewing the evidence in 1942, I⁶ ventured to point out that this concept had been built on plausible assumptions rather than on substantial experimental evidence. As a result of additional studies on patients and animals recently reviewed by Gregersen,⁷ this mechanism seems to have been discredited. In the most common forms of shock, reduction in blood volume occurs chiefly at the time of injury and the progressive circulatory failure which follows cannot be ascribed to a gradual decrease in blood volume. Obviously the defect must lie in the cardiovascular apparatus.

During the past six years my associates and I have elected to study the hemodynamics of hemorrhage and shock with the hope of elucidating especially the cardiovascular mechanisms involved in irreversibility, an inquiry which even exceeds in importance the establishment of initiating factors. During these studies we have repeatedly published results which raised the question whether, in our zeal to implicate peripheral mechanisms, myocardial depression may have been overlooked as a factor or its importance minimized. Suspicions that the myocardium may be depressed in shock have been voiced by a number of other competent investigators, among them Howell,⁸ Henderson,⁹ and Erlanger and Gasser.¹⁰ However, in view of immediately beneficial effects of infusions, they, as well as other authorities, did not regard the degree of myocardial depression of great importance. More recently other investigators¹¹⁻¹⁴ have laid greater stress on the existence and possible importance of myocardial damage, but the question whether cardiac filling and expulsion is really reduced at equivalent filling pressures has not been heretofore examined. This, in accordance with laws formulated by Henderson and Starling, would seem to be the supreme test.

This report attempts to summarize and integrate our evidence for the co-existence of myocardial depression in irreversible shock, obtained by different approaches to the problem.

METHODS

Standard Methods for Producing Hemorrhagic Shock.—Since the preponderance of evidence indicates that the most common forms of shock are initiated by reduction in effective circulating blood volume, the simplest and most controllable method for induction of shock should be by bleeding. However, at the inception of this work (1940) it had not proved possible to produce shock with certainty by bleeding; animals either died of cardiorespiratory failure or survived. As a result of many studies in other institutions as well as in our own, a number of standard procedures have been evolved to produce standardized hemorrhagic shock (for references, see Gregersen⁷). In general, these methods fall into two groups: (1) those employing withdrawal of a certain per cent of the estimated blood volume of animals and (2) those employing withdrawal of volumes sufficient to reduce arterial pressure to definite low levels. Many trials have shown that bleeding of animals on the basis of body weight is not practical because of many variables involved. Bleeding a certain percentage of the predetermined blood volume has proved more successful. Experience has shown that rather rapid bleeding until the blood volume is reduced to 40 to 48 per cent

of normal eventuates in hemorrhagic shock with fair consistency.⁷ While absolute figures are still not available, our recent studies on inferior cava flow indicate that such reduction in blood volume reduces total venous return to approximately one-fourth to one-sixth of the normal. However, corresponding reductions in venous return can be produced by smaller decreases of blood volume if other factors, such as operations and anesthesia, themselves operate to reduce venous return. Therefore, extreme care and caution must be exercised to prevent supervention of such factors which affect venous return. This somewhat limits use of the procedures in the study of cardiovascular dynamics of standard hemorrhagic shock. In such investigations which require the use of anesthesia and variable operative procedures, our procedure, based on many preliminary trials by Werle and myself,¹⁵ refined in association with Huizenga and Brofman,¹⁶ and now used in over 400 dogs by various groups, has proved more suitable in our hands.

The method consists briefly of the following steps: (1) bleeding of a dog from a femoral artery at a rate of about 50 c.c. per minute until arterial mean pressure is reduced to 50 mm. Hg; (2) maintenance of this pressure for ninety minutes, if necessary by additional small withdrawals of blood during the early period; (3) further reduction of arterial mean pressure to 30 mm. Hg by careful additional bleeding; (4) maintenance of arterial pressure at this critical level for forty-five minutes, giving small intravenous infusions toward the end of this period if necessary; (5) intravenous reinfusion of all blood withdrawn into heparin after filtration and warming, at a rate less than 50 c.c. per minute (this generally results in reasonable recovery of arterial pressure for periods of one-half to one hour); (6) observation of the development of shock which causes arterial pressures to fall progressively to 40 mm. Hg or less in three to six hours. These changes in mean arterial pressure are indicated in Fig. 2. This standard procedure not only serves to produce irreversible hemorrhagic shock, which has a fairly standard hemodynamic course in different dogs, but also *enables us to compare in the same animal the hemodynamic changes produced during states of hypovolemia (posthemorrhagic hypotension) with those that develop spontaneously during states of normovolemia (postinfusion failure)*. Comparison with controls in the same animals¹⁶ have shown that the average reduction in blood volume after postinfusion circulatory failure amounts to only 0.7 ± 1.64 c.c. per kilogram.

Anesthesia and Operative Procedures.—It is a primary requisite in experimental studies of shock that the condition produced shall be reasonably identical with that observed in various forms of shock in man. In 1942 I⁶ presented arguments that this can be accomplished best when dogs are properly anesthetized with morphine and barbitol. In the six years during which this anesthetic was used, our belief has been corroborated that experiments so performed are better standardized and permit more secure deductions than those performed under local or temporary ether anesthesia. An hour or two after induction of morphine-barbitol anesthesia, arterial and central venous pressures as well as cardiac output are fully equal to those reported by others on unanesthetized dogs.¹⁷ However, the use of continuous general anesthetics is still deplored by some investigators.

Gregresen⁷ has recently restated the following drawbacks to the use of anesthetized animals: (1) Since it is impossible to reproduce all clinical signs of shock during a state of anesthesia, it is difficult to be certain that comparable conditions have been produced. (2) This is possible by use of temporary ether anesthesia or, in certain types of experiments, local anesthesia. (3) Permanent anesthesia modifies compensatory reactions so that bodily changes differ quantitatively and qualitatively from those of the normal body. To these the following may be added: According to several reports,^{18,19} administration of morphine or barbital after hemorrhage or during impending shock intensifies the circulatory failure.

To these objections the following answers can be made categorically: (1) Unfortunately certain clinical signs, for example, sweating and pallor, are not observable in dogs, anesthetized or unanesthetized. Muscular tension and activity vary considerably in clinical cases of shock, and the characteristic facial expressions and general appearance of patients in shock also occur in other acute clinical states which do not eventuate in shock. The cardinal signs, reduction in cardiac output, arterial pressure, and peripheral blood flow, occur in barbitalized dogs as in clinical shock even after large transfusions. It is true that cardiac acceleration precedes initial changes of shock in barbitalized animals, but it is also true that few patients suffer injury or wounds without a preceding acceleration of their hearts due to psychic reactions or muscular effort. Finally, if anesthesia obscures signs of shock, it should likewise be difficult to recognize its occurrence in patients in the operating room—a view to which surgeons are not likely to subscribe. (2) Use of temporary ether anesthesia during infliction of injury or bleeding affects compensatory reflex responses more than does barbiturate anesthesia. It induces excessive hyperventilation and was probably responsible for low CO_2 content and pCO_2 of blood reported by the Columbia investigators.⁷ While local anesthesia or nerve block are unquestionably useful in the study of many shock problems, cerebral reactions develop in dogs during bleeding which cause whining, restlessness, struggling, irregular breathing, exacerbations of arterial pressure. These make it difficult or impossible to evaluate dynamic changes in the heart or circulation per se. (3) No experimental evidence exists for the statement that qualitative or quantitative differences occur in compensatory reactions during shock produced in unanesthetized and properly barbitalized dogs. As far as known, all the cardiovascular and respiratory reflexes evoked from somatic and visceral structures are present during morphine-barbital anesthesia. It has perhaps not been sufficiently emphasized that the changes in temperature regulation and blood concentration reported by Green and associates²⁰ from our laboratory are consequences of light barbiturate anesthesia, which is known to cause shivering or clonic muscular movements. It is true that the spleen is enormously engorged and, on excision, may yield 150 to 200 c.c. of blood in a dog weighing 10 kilograms, but it empties rather completely within fifteen minutes after a large hemorrhage and remains constricted throughout experiments such as ours.²¹ (4) Unquestionably any anesthetic, including morphine and barbital, administered *after* severe hemorrhage, exerts deleterious effects. However, given one and one-half to two hours previous

to experimental procedures, it renders dogs and guinea pigs more resistant to blood loss and posthemorrhagic hypotension.^{22,23}

While we feel satisfied that anesthesia introduces no serious problem, there can be no question that coincident operative procedures hasten and accentuate the development of shock. Our studies on the heart and circulation were therefore carried out as far as possible on animals submitted to very minor operative procedures. However, it proved necessary to extend these with experiments requiring exposure of the heart. In applying instrumentation primarily evolved to study acute reactions of the myocardium to experiments which extend over many hours and which, in addition, require artificial respiration and opening of the chest, it was necessary to evaluate the extent to which surgical "shock factors" complicate those due to hemorrhagic hypotension. Despite the fact that every known expedient was used to reduce such contributing factors, approximately half of such animals tolerated less loss of blood, withstood periods of 50 and 30 mm. Hg hypotension for shorter intervals, and developed post-infusion circulatory failure more rapidly. Fortunately, it was found that, if accidental occult hemorrhage after reinfusion of heparinized blood is avoided, comparable sequential dynamic states occur in operated and essentially unoperated dogs, the only difference being the speed with which reactions develop. However, when extensive operative procedures were required, we based our conclusions regarding myocardial impairment on those experiments in which the time courses, as well as arterial pulse patterns, most nearly corresponded with those of intact animals, rather than on statistical evaluation of all experiments, including those in which uncontrollable variables entered.

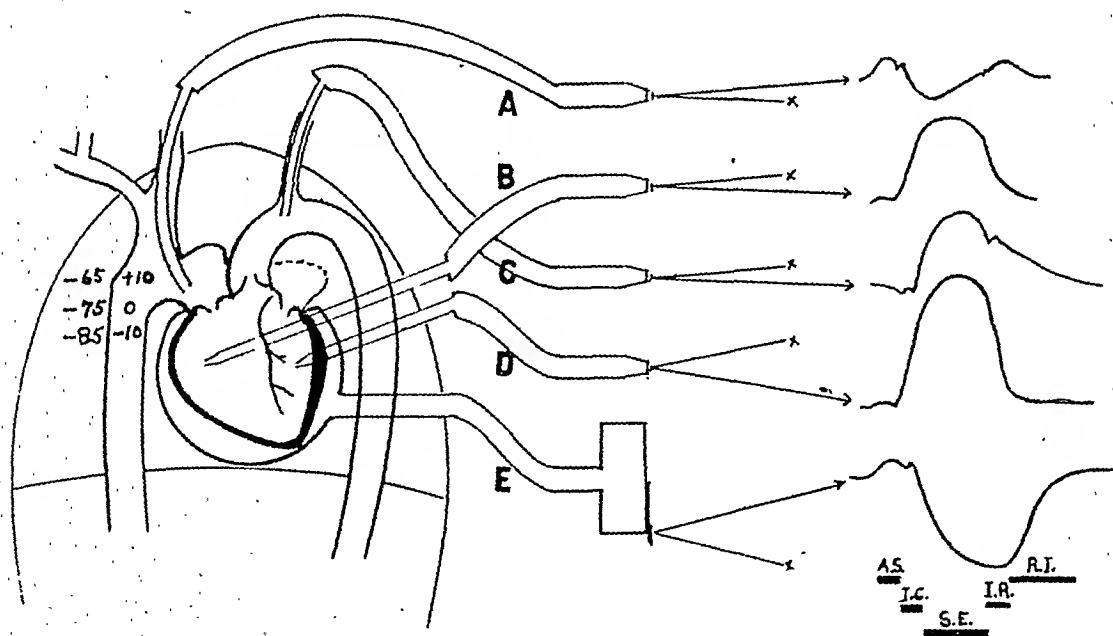


Fig. 1.—Scheme showing registration of dynamic changes of heart and representative curves under normal conditions. A, Pressure pulses of right atrium; B, same from right ventricle; C, same from left ventricle; D, same from aorta; E, volume curves of both ventricles. Records aligned at right with regard to phases of a heart cycle. A.S., atrial systole; I.C., isometric contraction; S.E., systolic ejection; I.R., isometric relaxation; R.I., rapid inflow. Numerals on right indicate how effective venous pressure remains at 75 mm. water under different intrathoracic pressures.

EVALUATION OF CARDIODYNAMIC CHANGES

Methods for Evaluating Cardiodynamic Changes.—While a number of special techniques were used for special studies, the standard experiments involved various combinations of recordings diagrammatized in Fig. 1. They included registration by calibrated optical manometers of adequate frequency of pressure pulses in the right atrium, *A*, right ventricle, *B*, aortic arch, *C*, and left ventricle, *D*. By placing a cardiometer around the ventricles, phasic volume changes were recorded by calibrated systems, *E*. The types of curves recorded by each of these recorders are also illustrated in Fig. 1 with correct temporal and ordinate relations. With an understanding of their meaning, as analyzed in most textbooks of physiology, and a knowledge of changes induced by known variables, such a chart of curves serves the physiologist much as a master score does the conductor of an orchestra.

Aortic Pressure Pulses.—These are useful (1) in determining systolic and diastolic pressures exactly, (2) in calculation of changes in duration of ventricular systole with respect to diastole (or heart rate), and (3) in evaluating altered mechanisms of cardiac ejection at different states of arterial tension by changes in their configuration.

The sequential changes which occur in amplitude, contour, and time relations of curves during the course of the standard experiments outlined previously have been established and repeatedly confirmed. They are illustrated in Fig. 2 with reference to mean arterial pressure changes. Beat 1 is a control. Reduction of mean arterial pressure to 50 mm. Hg, *A*, within ten minutes or less reduces systolic more than diastolic pressure and thereby decreases the pulse pressure. The pulse pattern (Beat 2) is characterized by abridgement of the period of systolic ejection, development of a primary spike which is followed by a peaked summit, and this by a deep incisura. Following this, the pressure gradient declines more gradually than in control pulses. As more blood is withdrawn to maintain a constant hypotensive level, *A-B*, the pulse pressure decreases somewhat more, and curves are characterized by a slower rise, simple rounded contour, and a flat diastolic pressure as shown in Beat 3. These changes merely become intensified during the 30 mm. period, *B-C*, as shown by Beat 4.

Upon completion of the reinfusion of all withdrawn blood, mean pressure is restored to levels which may be somewhat below or somewhat above control levels in different animals; but the pressure soon levels off, as indicated in Fig. 1, *D-E*, at a plateau level 85 to 90 per cent of control mean pressure. Immediately after infusion, normal patterns of arterial pulses are restored (Beat 5). However, during the plateau level of mean pressure, the arterial pressure pulses usually display some reversion to a form which suggests deterioration of cardiac action. This constitutes the first phase of circulatory failure. The changes (Beat 6) include redevelopment of a primary spike, a more peaked systolic summit, an abridged ejection phase, a deep incisura, and a lower postincisural pressure. Apparently, mean pressure is maintained through progressive cardiac acceleration and compensatory vascular mechanisms despite some decrease in cardiac output.

A second stage of circulatory failure begins from one-half to one and one-half hours after reinfusion, *E*, and is signaled by a progressive decline of mean pressure to about 70 per cent of control values. Toward the end of the period, *E-F*, pulse pressure has been reduced, and the pulse patterns (Beat 7) revert to the simple form observed after bleeding (see Beat 5). As systolic, diastolic, and pulse pressures slowly decrease thereafter, this deterioration in form is accentuated, as shown in Beats 8 and 9. It is apparent that the changes in central pulse patterns which follow abstraction of blood from the circulatory system and those which develop spontaneously after its replacement do not differ essentially. However, it may be noted in Fig. 2 that after reinfusion the stepwise deterioration in form occurs at somewhat higher diastolic pressure levels than after bleeding.

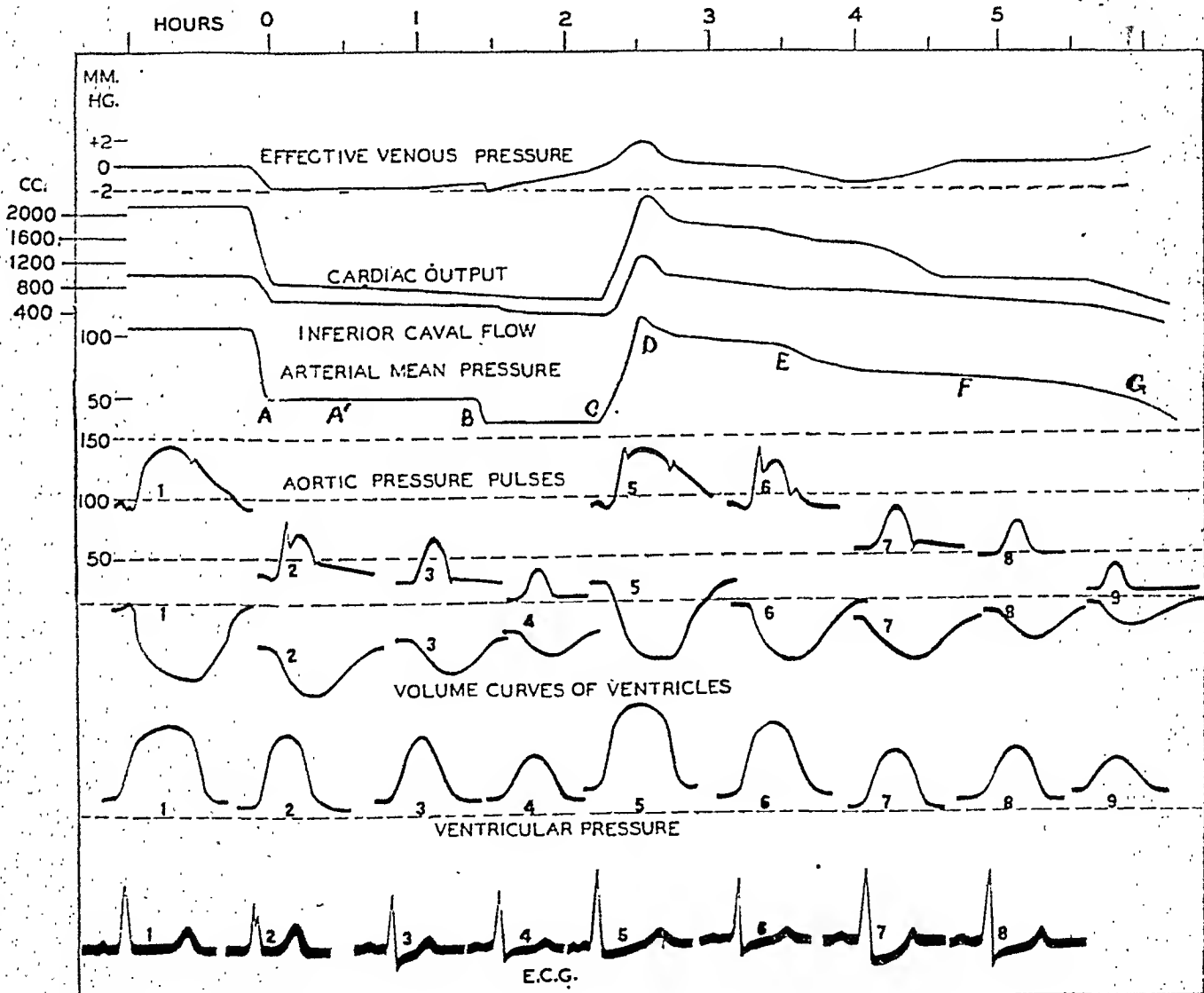


Fig. 2.—Chart interrelating cardiodynamic changes during hemorrhagic hypotension, reinfusion, and subsequent circulatory failure. Discussion in text.

Sequential Changes in Cardiac Output.—While it had been satisfactorily established that cardiac output decreases progressively both after hemorrhage and in various types of experimental shock,^{1-3,25,26} it remained to be demonstrated that postinfusion circulatory failure of our experiments was also accompanied

by such changes. In order to obviate difficulties inherent in application of the Fick principle to dogs²⁷ and to realize more frequent determinations of cardiac output than that method allows, H. C. Wiggers¹⁷ succeeded in eliminating certain faults in the Stewart method and in applying it to cardiac output determinations in intact dogs. Later, with Middleton,²⁸ the sequential changes in our standard experiments were established. The trend of these changes is indicated in Fig. 2. H. C. Wiggers and Middleton concluded that withdrawal of blood sufficient to reduce mean arterial pressure to 50 mm. Hg, *A*, promptly reduced cardiac output to 29 to 45 per cent of control values. Calculated stroke volume was more severely reduced during the latter part of this period because of the mechanical effect of cardiac acceleration. Only minor fluctuations occurred during the 30 mm. period, *B-C*. Following reinfusion of blood, *C-D*, cardiac output returned to or slightly exceeded control values in approximately one-half of the animals; it was restored to only 45 to 85 per cent of control values in the other half. Despite the fact that the circulating blood volume was almost equal to that at the start of the experiment,¹⁶ progressive reduction of cardiac output gradually supervened even while mean arterial pressure was maintained, *D-E*. Continuing reduction in cardiac output appeared to be responsible for the decline of arterial pressure to 65 to 80 per cent (average 70 per cent) of control figures, *E-F*. Thereafter cardiac output tended to stabilize, and further decline of mean arterial pressure to 30 per cent of control figures, *F-G*, was apparently due to reduction in total peripheral resistance. These results demonstrated that postinfusion circulatory failure, like experimental and clinical types of shock, is associated with progressive reduction in cardiac output. However, reduction in blood volume is not necessary to produce these typical changes.

Central Venous Pressures.—Since the extent of ventricular filling and the volume of cardiac output are primarily determined by the venous filling pressure, it might be anticipated that the central venous or atrial pressure would undergo a decline if reduction in cardiac output during hemorrhagic shock were due to decreased venous return alone. Since the heart and large intrathoracic veins are under subatmospheric pressure, the atrial pressure available for right ventricular filling is not measured by pressure recorders balanced against atmospheric pressure; it must be calculated as the algebraic difference between such pressure and intrathoracic negative pressure measured at the same time; that is, by the effective venous pressure. Thus, as illustrated in Fig. 1, an effective venous pressure of say 75 mm. saline could be created with highly variable intra-atrial pressures. The estimation of effective venous pressure is especially important in these studies, for, as found in our early studies,^{16,29} intrathoracic pressure changes significantly during bleeding and reinfusion. We also realized early that exact measurement of central venous pressure and calculation of effective venous pressure is not the simple procedure that it is generally believed to be. Considered judgment as to points of measurement, in addition to fidelity in registration, is important. In our first studies²⁹ we measured venous pressure of optical pressure records just before ventricular systole (*Z* on atrial curve of Fig. 3) and determined intrathoracic mediastinal pressure *at the same moment during expiratory*

rest. It was found after bleeding that recorded and effective venous pressures both decreased definitely but not proportionately; both tended to rise slightly during the period of drastic hemorrhagic hypotension (Fig. 2, B-C). During the postinfusional failure, decline of arterial pressures (Fig. 2, E-G) and deterioration of pressure pulses occurred *without decrease in effective venous pressure below control levels* in eight of twelve experiments. This suggested that any tendency for venous return to decrease may be nicely counterbalanced by decrease in cardiac output, which, if true, suggests primary myocardial depression.

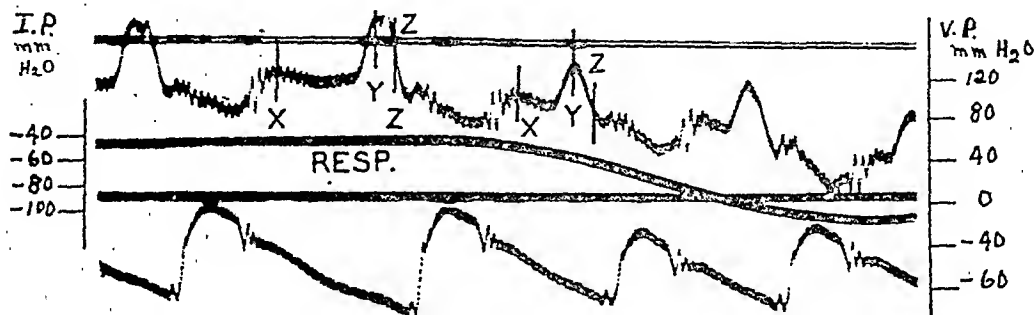


Fig. 3.—Pressure pulses from right atrium (upper curve) and aorta (lower curve) of a normal dog, related to intrathoracic pressure changes recorded by a calibrated air manometer. Inspiration, downward movement. Upper curves show the considerable phasic variations which exist during cardiac cycles and the still greater variations due to respiration. The importance of selecting fixed points or obtaining average pressure during expiratory rest is evident.

The changes in effective venous pressure were again studied in thirty-five dogs after our procedure for producing hemorrhagic shock had been better perfected.¹⁶ In this research, *average venous pressures during an expiratory phase* were used in calculations of effective venous pressure. The experiments in which postinfusion circulatory failure was accompanied by reduced and essentially normal effective venous pressures were divided approximately equally. It appeared obvious that the decline of arterial pressure, reduction of cardiac output, and deterioration of arterial pressure pulses after transfusion is sometimes, but not necessarily, accompanied by a decline of recorded and effective venous pressures.

Establishment of the trend of effective venous pressures seemed so important that measurements of intrathoracic and venous pressures were continued in forty-eight more experiments in which other circulatory phenomena were under investigation. Comparisons between control effective venous pressures and those which developed at different comparable periods of experiments were made.³⁰ It suffices for present purposes to recall that when arterial pressure had again declined to 50 mm. after reinfusion, effective venous pressures were below control values in eighteen dogs only; they were near or above control values in thirty dogs. Indeed, the lowest effective venous pressure of the latter group was 60 mm. saline, a value commonly regarded as normal for dogs.

While the principle for determining effective venous pressures is sound, the possibility exists that technical errors can be introduced in determination of intrathoracic pressure; for example, by development of air pockets of varying

size in the pleural cavity or in other regions of the thorax. To check this contingency, twelve supplementary experiments were performed³⁰ on dogs with an effective pneumothorax under mild artificial respiration. Under these conditions the central venous pressure actually recorded represents the effective filling pressure. The results showed a decrease in right atrial pressure in nine and approximately normal pressure levels in only three animals. For reasons analyzed at the time, the latter three were regarded as experiments which most nearly represented conditions in unoperated dogs, but this need not be stressed at the present time. If we add the experiments just reviewed, we find that during post-infusion shock effective venous pressure decreased in forty-eight animals and was essentially at normal levels in fifty-nine. This dominant trend is indicated in Fig. 1. Of special interest are the decline of effective venous pressure during *A-B*, the tendency to return toward normal during *B-C*, the supernormal elevation at *D*, the stabilization during *D-E*, the decline during *E-F*, and the ultimate rise during *F-G*. The fact that the progressive circulatory failure following transfusion occurred in so large a per cent of animals without significant reduction in effective venous pressure strongly suggested that myocardial depression supervened in the majority of our animals submitted only to minor operative procedure. It was important, however, to substantiate such deductions by more direct evidence and to elucidate the cardiac mechanism by which reduction in output is brought about in postinfusion shock.

Cardiometer Experiments.—Werle and I³¹ studied the alterations in diastolic size, filling, and discharge of the ventricles by means of cardiometers during the course of similar hemorrhage experiments. Typical volume curves recorded optically at different times showed that stroke volumes and minute volumes were decreased consistently during both the periods of hemorrhagic hypotension and of shock following infusion, but the manner in which such reductions occurred in the latter period differed. In one group of animals (approximately half), reduction in stroke volume was accompanied by decrease in atrial pressure, reduced rate of ventricular filling, and decreased diastolic size at comparable heart rates. These resembled the effects produced by simple bleeding. In the other 50 per cent of experiments illustrated by volume curves in Fig. 2, atrial pressures during postinfusion failure were above control values and the diastolic size of the ventricles was greater, but the ventricular filling rate was still retarded. In these experiments it was also observed that diastolic size became greater during the period of 30 mm. Hg hypotension, while systolic discharge diminished (Fig. 2, volume curves 2, 3, and 4). Since myocardial depression apparently occurred in this half of the experiments, the question arose as to whether existence of a similar myocardial depression might be masked in the other group of experiments in which central venous pressures decreased. It should be added parenthetically that since diastolic size is also a function of duration of diastolic filling (that is, heart rate), all of these conclusions are actually based on reconstruction of volume curves for identical heart rates. This cannot be depicted in the diagrams without disturbance of the correct time relations to other curves.

Investigators have been accustomed to infer that the myocardium is unaffected in shock because of repeated demonstrations that cardiac output can be restored by transfusions. However, it had not been demonstrated, as required by Starling's law, that such restoration of cardiac output occurs at normal venous pressures. That this is not true after prolonged hypotension was shown in two ways in our experiments: (1) Normal cardiac output or stroke volumes at equivalent heart rates after reinfusion occur only while venous pressures are far above control values; it is less when these return to control values (Fig. 2, volume curves 5 and 6). (2) When small rapid transfusions were given just previous to final infusion at C, or when added transfusions were given during final circulatory failure, E-G, they restored control venous pressures temporarily, but systolic discharge remained below that during initial controls.

In order to study this response under more controllable venous pressures, Wegria, Guevara Rojas, and I⁵² devised a heart-lung dog preparation. Among other observations it was established that a period of 50 min. hypotension lasting for one to one and one-half hours decreases the ability of the ventricles to respond to equivalent venous pressures.

Ventricular Pressure Curves.—Opdyke and I⁵³ studied the changes in right ventricular pressures of intact animals and later compared changes in right and left ventricular pressures in exposed hearts during the course of hemorrhagic hypotension and shock. In records so obtained, conclusive evidence that myocardial depression occurs would be furnished if, either during the irreversible period of hemorrhagic hypotension or during postinfusion failure, initial tension increased while systolic ventricular pressure and systolic discharge decreased. This occurred in right ventricular pressure curves recorded from intact animals during later periods of prolonged hypotension as well as during postinfusion failure. Since the changes in initial tension correlated with alterations in effective venous pressure in the greatest number of animals, a few of these curves are reproduced in Fig. 2. However, since such changes might have resulted from uncontrollable variations of intrathoracic pressure or shifts in hydrostatic levels of the right ventricle, they cannot be regarded as quite conclusive. For this reason, further experiments were conducted on exposed hearts in which environmental pressure and hydrostatic positions of the ventricles could be kept constant. Unfortunately, it was not possible to record two curves on 12 cm. paper with sufficient amplitude, so that we could not always be certain of the existence of small differences in initial tension. However, records from five good experiments were meticulously measured and rechecked and an average curve constructed. This average curve showed clearly that initial tensions decrease in both ventricles after simple hemorrhage, but that initial tensions remain approximately at control levels during postinfusion failure when cardiac output has presumably decreased to an equivalent extent, as after bleeding. However, in an experiment considered to be our best, initial tensions declined during this period, just as after simple hemorrhage.

While these studies failed to settle the question as to whether the decreased ventricular force and discharge during postinfusion failure is associated with

unchanged or elevated initial tension, the changes in contour of the curves contributed to our understanding of the altered cardiodynamics. The alterations will be considered later.

Blood Flow in the Inferior Vena Cava.—Eckstein and associates,³¹ in a series of thirteen experiments, recorded inferior cava flow by a differential pressure type of flowmeter. The trends of flow changes charted in Fig. 2 follow alterations in cardiac output determined in intact dogs in a general way. A similar correspondence in trends occurred between inferior cava flow and central venous pressure. Two exceptions must, however, be noted: (1) There appeared to be a lag in the elevation of central venous pressures and only a minor increase in cava flow until about one-fifth to one-fourth of the total blood withdrawn had been reinfused into the femoral vein. (2) During the late period of posthemorrhagic hypotension, *B-C*, and the second stage of postinfusion failure, *F-G*, inferior cava flow continued to decrease, but central venous pressures tended to stabilize or rose slowly toward normal levels. Inferior cava flow was consistently related to venous pressure gradients between the lower region of the inferior cava and right atrium but not necessarily to central venous pressure.

✓ *Electrocardiograms.*—If, as appears probable from cardiodynamic studies, impairment of the myocardium is a factor in the unfavorable response to blood transfusion, it is reasonable to expect that a methodical series of electrocardiograms might reveal some changes. Manrique Izquieta and Pasternack²⁵ studied the configuration of electrocardiograms obtained by three standard leads and six chest leads paired with a central terminal. Displacement of the S-T segment in several leads, particularly in V_2 and V_3 , and less often in Leads II and III, occurred during the late periods of hypotension (Fig. 2, electrocardiogram complexes 3 and 4). The electrocardiogram usually became normal again after infusion, but before arterial pressure had declined significantly, S-T displacement reappeared and the T waves often became larger and peaked (Fig. 2, electrocardiogram complexes 6, 7, and 8). ✓

ANALYSIS OF RESULTS

In the previous section the experimental work was briefly reviewed, from which the underlying data assembled in Fig. 2 were derived. In the event of experimental discrepancies, reasons were given for the choice of exhibits. We shall now proceed to a vertical analysis of various periods of our experiments and attempt to formulate conceptions of the cardiodynamic mechanisms concerned.

✓ *Effects of Simple Hemorrhage.*—The cardiodynamic effects produced by simple severe hemorrhage are exhibited during the first twenty or thirty minutes of the 50 mm. hypotension period, *A-A'*. All the changes which occur during this interval are usually reversible by reinfusion of substantial volumes of blood, plasma, or blood substitutes. In many cases isotonic saline infusion suffices to produce survival.

The low systolic and diastolic pressures and small pulse pressure (see Beats 1 and 2) are due to decreased systolic discharge and reduced minute output. This reduction, in turn, is secondary to decreased venous return. Inferior vena cava flow diminishes to 45 per cent of normal or less, actual and effective central venous pressures fall significantly, initial tension in the ventricles is decreased, and their diastolic size is less (see Beats 1 and 2). The changes in configuration of central pressure pulses already described are due to alterations in the mechanism of left ventricular ejection. Ventricular volume and pressure curves clearly show that duration of systole is less and that the ventricles expel their diminished contents in a shorter time, but still with good velocity and force. This sudden ejection into a lax aorta produces the characteristic overshoot of arterial pressure (Beat 2). However, the greatly diminished stroke volume is insufficient to maintain aortic pressure even during systole; pressure falls considerably toward the end of systole, the incisura after completion of systole is deep, and the diastolic portion is low. Electrocardiograms taken during this period reveal no changes which cannot be attributed to physical changes in the size and position of the heart after bleeding.

Effects of Oligemic Shock.—The succeeding 105 to 115 minutes of hypotension; *A'-C*, represent a period during which irreversible changes are produced. The cardiodynamic alterations are characteristic of progressive and terminal stages of shock associated with low blood volumes; that is, *oligemic shock*. If untreated, animals die of cardiorespiratory failure; if substantial transfusions are given, complete immediate recovery apparently occurs, but this is temporary and usually followed by slow progressive decline of arterial pressure and death. Previous to infusion, systolic and diastolic pressures do not change materially until further bleeding to 30 mm. Hg levels, *B-C*; occasionally systolic, diastolic, and pulse pressures decrease spontaneously without additional bleeding.

Reduced venous return indicated by further diminution of inferior cava flow could account for the further reduction of cardiac output and pulse pressure which obviously occurs during this stage of hypotension. However, examination of other occurrences indicates that cardiodynamic mechanisms are otherwise affected. Effective venous pressure, initial ventricular tension, and diastolic ventricular size all tend to return toward normal during the interval *B-C* instead of decreasing, as may be anticipated from effects of diminished inferior cava flow. Comparison of Beats 3 and 4 with Beat 2 shows that ventricular pressure curves rise more slowly, denoting that the force of contraction is decreasing; volume curves not only exhibit some increase in diastolic size and reduced strokes, but also a slower velocity of ejection. This lazy ventricular action accounts for the slower rise and rounded form of arterial pulse patterns in Beats 3 and 4. The systolic discharge is not sufficient to sustain diastolic pressure which remains at a low flat level. Such pressure pulses are diagnostic of stroke volumes barely sufficient to maintain any circulation. The deduction that myocardial depression has supervened is confirmed by appearance of S-T segment depression in electrocardiograms and by the fact that such hearts do not respond with normal stroke volumes when atrial pressure is temporarily raised to normal levels.

Immediate Effects of Infusion.—Immediately after reinfusion of all withdrawn blood at a rate of about 50 c.c. per minute, *C-D*, a large pressure difference exists between the inferior vena cava and the right atrium. The abdominal veins become a reservoir from which increased volumes of blood are delivered to the heart for five to fifteen minutes after infusion. Restoration of arterial pressures and forms of pressure pulses to normal are the most obvious effects. Intraventricular pressures of normal amplitude, contour, and duration redevelop; as a rule, the electrocardiogram again becomes normal. In the most successful experiments, cardiac output also returns to control values. However, all data show that, in order to produce these effects, the ventricles are required to operate under supernormal venous pressures and initial pressures compared with controls (see Beats 1 and 5). Inferior cava flow is increased over normal, effective venous pressure and initial tension are much elevated, and the diastolic ventricular size is tremendously increased. However, the stroke volume at equivalent heart rates is not greater than in control states. The ventricles are maintaining normal systolic discharges and output only because they are overstretched, a condition characteristic of incipient myocardial failure.

Normovolemic Postinfusion Shock.—The circulatory failure which develops after reinfusion usually occurs in three fairly distinct stages: *D-E*, *E-F*, *F-G*. The cardiovascular changes which develop during these stages characterize a type of shock which develops without significant reduction in blood volume; they are due solely to irreparable damage to the peripheral vessels, the heart, or both. It may, therefore, be designated *normovolemic shock*. The sequential hemodynamic changes deserve careful study, because they may have application to clinical forms of shock in which significant oligemia does not appear to exist, or in which shock develops despite restoration of a normal blood volume by transfusions.

Within fifteen minutes after reinfusion, inferior cava flow has returned to normal levels, but central venous pressures and initial tension in the ventricles still remain above control values. During the next ten or fifteen minutes cava flow and cardiac output are decreased materially. Comparison of Beats 5 and 6 reveals that the diastolic ventricular size is normal but the stroke volume is less. Ventricular pressure curves start with normal initial tensions and assume a rounded contour; the maximum intraventricular pressure is reduced, and systole is shortened. In short, the changes in cardiac behavior observed after simple hemorrhage with much greater reduction in venous return and with a marked decline of central venous and initial ventricular pressures now develop when these are essentially at normal levels. Electrocardiograms taken at this time reveal the reappearance of S-T segment depression. Despite this obvious depression of myocardial function, mean-arterial pressure is maintained rather well, presumably through cardiac acceleration and continued viability of compensatory vascular mechanisms. However, arterial pressure pulses already mirror changes in the cardiac mechanism by changes in contour. These include redevelopment of a primary spike, a peaked summit in the abridged ejection phase, a deep incisura, and a lower postincisural pressure.

A second stage begins from one-half to one and one-half hours after reinfusion, *E-F*. It is signaled by a progressive decline of mean pressure to about 70 mm. and is due to progressive reduction in cardiac output. Inferior cava flow, effective venous pressure, initial pressures, and diastolic ventricular size all progressively decrease below control levels. Comparison of Beat 7 with Beat 6 shows the stroke volume is less and the velocity of ejection slower. Ventricular pressure curves display a slower rise and a lower maximum, indicating reduced force of contraction, and S-T segments of electrocardiograms continue to show displacement. Since all of these changes occur with reduction in venous return and effective venous pressure, any existing myocardial depression would tend to be obscured by concurrent reduction of venous return. However, *if normal venous flow and pressure are restored at this time by additional reinfusions, the stroke volume and cardiac output still remain below control values.*

A third stage is inaugurated about thirty minutes later by a further decline of arterial pressure and further deterioration of arterial pressure pulses, *F-G*. Since venous and initial pressures tend to rise while cardiac output becomes fairly stabilized, and the calculated total peripheral resistance is reduced, this decline appears to be chiefly of peripheral origin. The ventricles maintain their constant reduced output and force of contraction for a while by virtue of increasing diastolic stretch and initial tension. Ultimate failure of the heart comes about through development of deceleration and fairly great slowing. This reduces the cardiac output and arterial pressures very rapidly to low levels. When these are not sufficient to maintain activity of the respiratory center, death supervenes.✓

DISCUSSION

✓In the type of experiment outlined at the start, a protracted period of post-hemorrhagic hypotension produces irreversible changes which affect the myocardium as well as other organs. As a result of such myocardial depression, reinfusion of all withdrawn blood restores cardiac output, arterial pressures, and contours of pressure pulses only because venous return, effective venous pressures, initial ventricular pressures, and diastolic stretch of the ventricles greatly exceed those normally operative. As soon as these decrease to normal levels, cardiac output and stroke volumes diminish. Arterial pressures are stabilized for a time due to compensatory vascular mechanisms. This state of myocardial depression continues and is probably intensified during spontaneous circulatory failure which follows infusions, *but it is not the dominant factor responsible for progressive reduction of cardiac output, decline of arterial pressures, and deterioration of pressure pulse patterns.* As after simple hemorrhage, progressive reduction in venous return is the paramount factor. However, coexistence of myocardial depression is certainly not favorable, for it reduces the capacity of the ventricles to expel their diminished blood volumes as effectively as after simple bleeding. Consequently, myocardial depression plays an important role in the rapid downward trend of blood pressure and is the ultimate cause of death.

It cannot be claimed that myocardial depression, similar to that found in our types of experiments, exists in all states of shock. Our evidence does suggest,

however, that a study of myocardial function in shock deserves more careful exploration by cardiologists than has hitherto been given to this aspect of the shock problem. Myocardial depression is a subtle phenomenon and often an occult one even under otherwise normal conditions of the circulation. This is so because compensatory mechanisms operate automatically to maintain normal volumes of systolic discharge and cardiac output. However, as Starling tried so hard to emphasize, such hearts are laboring under a continued strain and nearer to their reserve limit. If, at the time of any shock-producing catastrophe, these reserve mechanisms are already utilized, the superposition of a reduction in venous return after a fairly rapid loss of blood or plasma may be expected to cause an earlier and more rapid development of myocardial depression. Since the functional state of the myocardium and the capacity of coronary response antecedent to shock-producing catastrophes unquestionably vary in dogs as well as in man, it is not surprising that the degree to which myocardial depression contributes to circulatory failure varies considerably. Since cardiodynamic studies have shown that myocardial depression can be a grave subsidiary factor, the problem merits further attention of cardiologists. The possibility that proper cardiac stimulants used in proper dosage and at the proper time may reverse the circulatory failure when transfusions fail to do so should not be regarded as a closed problem. ✓

SUMMARY

✓ The question as to whether myocardial depression occurs in hemorrhagic shock and, if so, its importance was reinvestigated. For this purpose the cardiodynamic changes which occur after simple hemorrhage, during prolonged hypotension (50 to 30 mm. Hg), during reinfusion of all the withdrawn blood, and during spontaneous circulatory failure following infusion, were studied in the same animal. In different series of experiments in which the same standard technique was used, we studied changes in calibrated arterial pressure pulses, cardiac output by a modified Stewart method, alterations in effective venous pressure, ventricular volume and pressure curves, inferior vena cava flow, and electrocardiograms by standard and chest leads.

Following simple hemorrhage sufficient to reduce mean arterial pressure to 50 mm. Hg, the changes in ventricular action are all secondary to reduction in venous return and decrease in effective central venous pressure. Electrocardiograms reveal no significant changes. Changes in the contour of the central arterial pulse consist in abridgement of the period of systolic ejection and development of a primary spike followed by a peaked summit, and this is followed by a deep incisura. As a result of decreased venous pressure, ventricular filling is slower, initial tensions decrease in both ventricles, and their diastolic size is smaller. Pressure and volume curves indicate that the ventricles expel their diminished volumes with good velocity.

If severe posthemorrhagic hypotension is prolonged for 135 minutes, death results from an oligemic type of failure unless blood is reinfused. However, such reinfusion is of only temporary benefit; a slow spontaneous circulatory failure and eventually death follow. Irreversibility develops during the period of pro-

longed hypotension. This includes depression of the myocardium, for while venous return continues to decrease slightly, effective venous and initial ventricular pressures return to or above control levels and the diastolic size of the ventricles augment. Nevertheless, the stroke volume and cardiac output decrease. Myocardial depression is further indicated by a subminimal stroke volume when venous pressures are elevated to normal levels and by development of S-T depression in electrocardiograms.

Reinfusion of blood restores arterial pressures and pulses as well as cardiac output to normal, but in order to do so the ventricles are required to operate under supernormal conditions of high venous pressure and initial tensions. As soon as these re-establish at normal levels, cardiac output decreases, and the ventricles pump less efficiently due to a depressed state of the myocardium. As arterial pressure declines to ca. 70 mm. Hg, reduction in venous return becomes so great that the myocardial depression is obscured but is detectable by special tests. A progressive circulatory failure develops despite the fact that blood volumes are not significantly decreased. This represents a form of *normovolemic shock* due solely to default of the peripheral circulation and of the myocardium. The predution of venous return is of paramount importance, but circulatory failure is hastened by coexistent myocardial depression.

Since the functional state of the myocardium and the capacity of the coronary responses at the time of shock-producing catastrophies may often be below par, myocardial depression may play as significant a subsidiary role in some cases of human shock as it did in our animals submitted to a particular type of hemorrhage and shock. The problem deserves further careful exploration by cardiologists.

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KENT'S FIBERS AND THE A-V PARASPECIFIC CONDUCTION THROUGH THE UPPER CONNECTIONS OF THE BUNDLE OF HIS-TAWARA

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AT THE end of the last century the "myogenists," who considered cardiac contraction to be a peristaltic wave, still had to do away with one obstacle before seeing the triumph of their conception. The "neurogenists" opposed them with an argument that seemed final: in the heart of man the auricles are separated from the ventricles by an inert conjunctive ring which makes it impossible for the wave of auricular contraction to reach the ventricles.

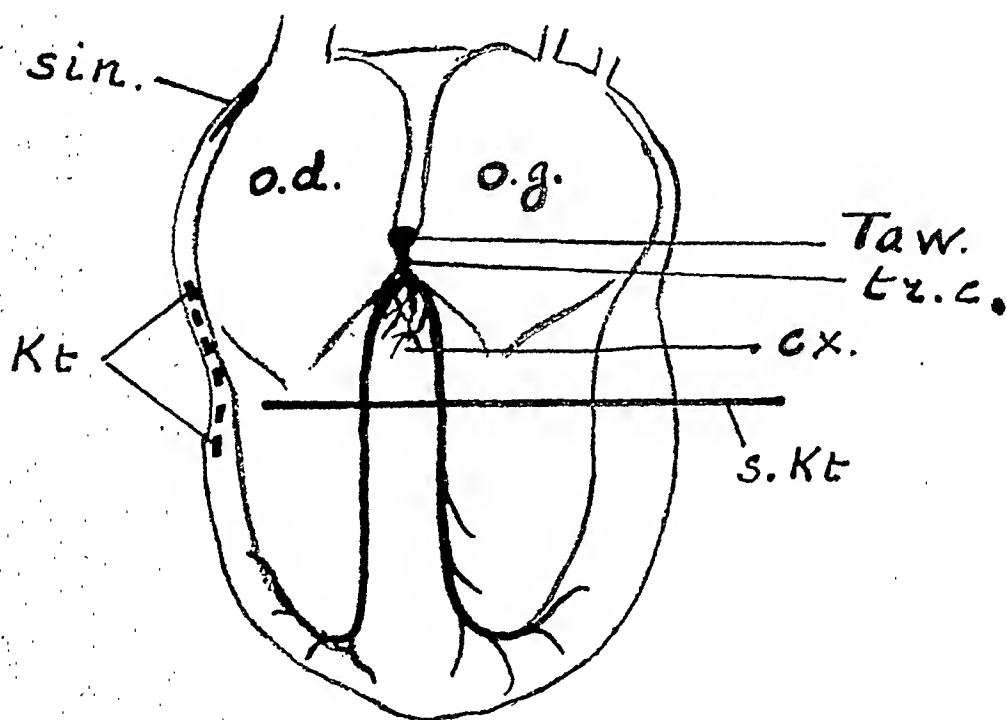


Fig. 1.—Scheme of the bundle of His-Tawara with the node of Tawara, *Taw.*, the main trunk, *tr.c.* and the Kent's fibers, *Kt*. The transverse line, *s.Kt*, represents the experimental section performed by Kent. The upper connections are represented by *cx.*

It was to remove this obstacle that His and Kent sought to discover a muscular bridge, a contractile hyphen between the auricles and ventricles of the human heart. They published their results simultaneously in 1893, independently

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of one another. His discovered the hyphen in the membranous septum, and what he found corresponds to what is known today as the main trunk of the bundle of His-Tawara. However, it was not until thirteen years later that this discovery came to light in Tawara's monograph (1906). Since then, the bundle of His has been considered as a complete organ consisting of specific tissue and having its particular physiology and pathology.

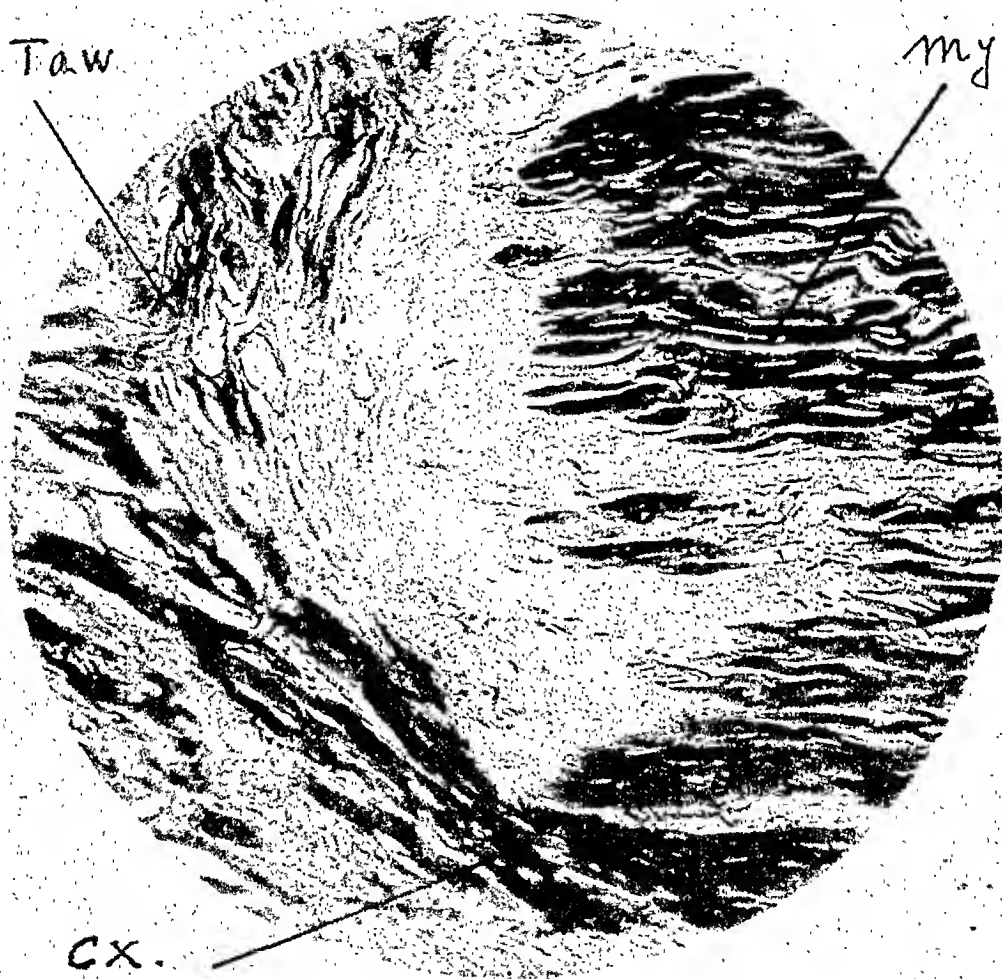


Fig. 2.—Large connection, *cx.*, uniting the node of Tawara, *Taw*, with the myocardial septum, *my*, in man.

Not as much can be said about Kent's fibers, which have never been made the object of a systematic description nor of a monograph. Following his first publication, Kent remained silent for twenty years. In 1913, he returned to the question when he published some few figures and reported certain experimental observations. In the earliest studies the fibers of Kent were represented as being small myocardial fasciculi joining the auricles to the ventricles in the regions of the lateral walls of the heart. In 1913, Kent no longer insisted on the left lateral fibers, but sought to identify a right lateral bundle uniting the right

auricle to the right ventricle. To confirm its function, he carried out a decisive experiment which consisted of severing the heart transversely in the horizontal plane, thus sectioning the interventricular septum with the two branches of the bundle of His-Tawara and leaving intact only the right lateral region (Fig. 1, s: *Kt*) where the so-called right lateral bundle was thought to be located. Kent concluded that, under these circumstances, it was this bundle, and it alone, which permitted a contractile wave to pass from auricles to ventricles.

Kent's experiments are described in a very summary manner. What is more important is that, even though correctly conducted, they were not adequate to resolve the question. When the experiments were made, Kent ignored a cause of error, on which I will present a few precise remarks.

According to the works of Tawara and those of Mönckeberg, it was believed that the main trunk and the two branches were isolated in a conjunctive retaining "muff". In 1932 I described the upper connections which unite the origin of the left branch to the upper part of the interventricular septum. I have found them again with Benatt, and later studied them experimentally with the aid of Rothberger in Vienna. These last findings have been published in detail with Winston (1941). Aschoff and Meesen, finally, have confirmed their existence. Fig. 2 represents one of these connections, particularly large, which unites the anterior and inferior part of the nodes of Tawara to the myocardial septum.

If we consider again the schema in Fig. 1 representing Kent's experiment, we understand without difficulty that the right lateral bundle of Kent is not alone in being able to conduct the wave of excitation from the auricle to the ventricle. This excitation may pass to the two ventricles through the upper connections above Kent's section.

If conduction by Kent's fibers is accepted (and it has still not been proved that these fibers exist regularly, and one can even doubt it), it should be regarded as an accessory form of conduction: paraspecific conduction.

Paraspecific conduction recognizes the contradictions which are manifest in the anatomicoclinical researches on bundle branch block. I will not dwell on this here. It applies, perhaps, also to the syndrome of Wolff-Parkinson-White, as Lequime and his collaborators have suggested.

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THE EFFECT OF SMOKING ON THE VASODILATATION PRODUCED BY THE ORAL ADMINISTRATION OF 95 PER CENT ETHYL ALCOHOL OR A SUBSTANTIAL MEAL

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INVESTIGATORS have inquired whether the oral administration of alcohol or the ingestion of a substantial meal will prevent the constriction of peripheral blood vessels known to be produced by the smoking of tobacco. Heberden¹ in 1802 first suggested the efficiency of alcoholic beverages in relief of angina pectoris, perhaps because they seemed to be vasodilators of no mean degree. In 1910 Brooks² observed in animals a rise in blood pressure and pulse rate immediately after the ingestion of alcohol with a subsequent lowering of blood pressure and increase of heart rate. In man, Lieb³ gave not more than 10 c.c. of whisky orally and found only slight changes in the blood pressure and pulse rate and these only after absorption had taken place. Grollman⁴ gave 35 c.c. of 95 per cent ethyl alcohol orally to normal persons and observed an increase in the blood pressure, pulse rate, and cardiac output within fifteen to thirty-five minutes after the ingestion of the alcohol. He believed this was secondary to the peripheral vasodilatation.

In 1932, Cook and Brown⁵ demonstrated, by measurement of skin temperature of the extremities, that oral administration of 95 per cent ethyl alcohol would produce vasodilatation of the peripheral blood vessels in both normal persons and in some individuals suffering from peripheral vascular disease. This vasodilatation lasted two hours or more. We have demonstrated that a substantial meal would give a similar result.^{6,7} We have shown, also, that irrespective of existing vasodilatation from the oral administration of alcohol, the degree of vasoconstriction induced in the usual cold pressor test was not altered significantly.⁸ With this background, we set out to try to answer the query of investigators with which this presentation opened.

PROCEDURE

The measurement of vasoconstriction and vasodilatation of the extremities was made by determination of the skin temperature of the fingers and toes, together with simultaneous observations of blood pressure and pulse rate.

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The observations were made on sixty-five normal persons, six women and fifty-nine men, whose ages ranged from 19 to 59 years, and whose basal metabolic rates ranged from -21 to $+5$ per cent. Many of them were physicians. All were habitual smokers and inhaled the smoke.

Data were obtained in a room in which the constant temperature was 25.5°C . (78°F .) and the relative humidity was 40 per cent. The subjects fasted for fifteen hours before the tests and, during the tests, they wore lightweight short pajamas and lay supine on comfortable beds.

The temperature of the plantar surfaces of the first and third toes of both feet and the volar sides of the distal phalanges of the first and third fingers of both hands were measured by means of thermocouples of copper and constantan. Generally, after a control period of about an hour, when fairly constant readings of the cutaneous temperature had been obtained and determinations of basal blood pressure and pulse rate had been made, smoking was begun. Two-thirds of two cigarettes of a standard brand were smoked in succession. Simultaneous determinations of blood pressure, pulse rate, and cutaneous temperature were obtained at intervals of one minute during the smoking, which generally lasted about twelve to sixteen minutes. The subjects inhaled the smoke at the depth and frequency customary with them. An attempt was made to eliminate all unnecessary noise and other stimuli which might produce vasoconstriction during this period. The procedure described established whether the subjects' blood vessels became constricted during smoking and, if so, to what degree.

On the same day that this preliminary test of the effects of smoking had been completed, or on another day shortly thereafter, 30 c.c. of 95 per cent ethyl alcohol in 250 c.c. of fruit juice was administered by mouth. After vasodilatation had become evident as an increase of the skin temperature of the toes and fingers, the subjects smoked two-thirds of two cigarettes. During the smoking, blood pressure and pulse rates were noted at intervals of one minute, as previously.

The same procedure was followed before and after the taking of a substantial meal.

RESULTS

One hundred twenty-one tests were made on the sixty-five subjects; in eighty-seven of these tests alcohol was employed, while in thirty-four food was used. Some of the same subjects were given food at one time and alcohol at another.

In one subject smoking before the ingestion of alcohol produced a considerable increase in the pulse rate, a small but definite increase in both systolic and diastolic blood pressure, and a definite decrease in the skin temperature of the fingers and toes. The decrease in the skin temperature was greater in the toes and of longer duration (Fig. 1).

Forty minutes after the ingestion of alcohol, evidence of vasodilatation was present and smoking was repeated. The effect was similar to that of smoking before the ingestion of alcohol except that the skin temperature of the toes and fingers did not decrease (Fig. 1). This observation indicates at least partial

inhibition by the alcohol of the vasoconstriction ordinarily produced by smoking. This result, however, was obtained in only one of the sixty-five subjects and this one had a basal metabolic rate of +1 per cent.

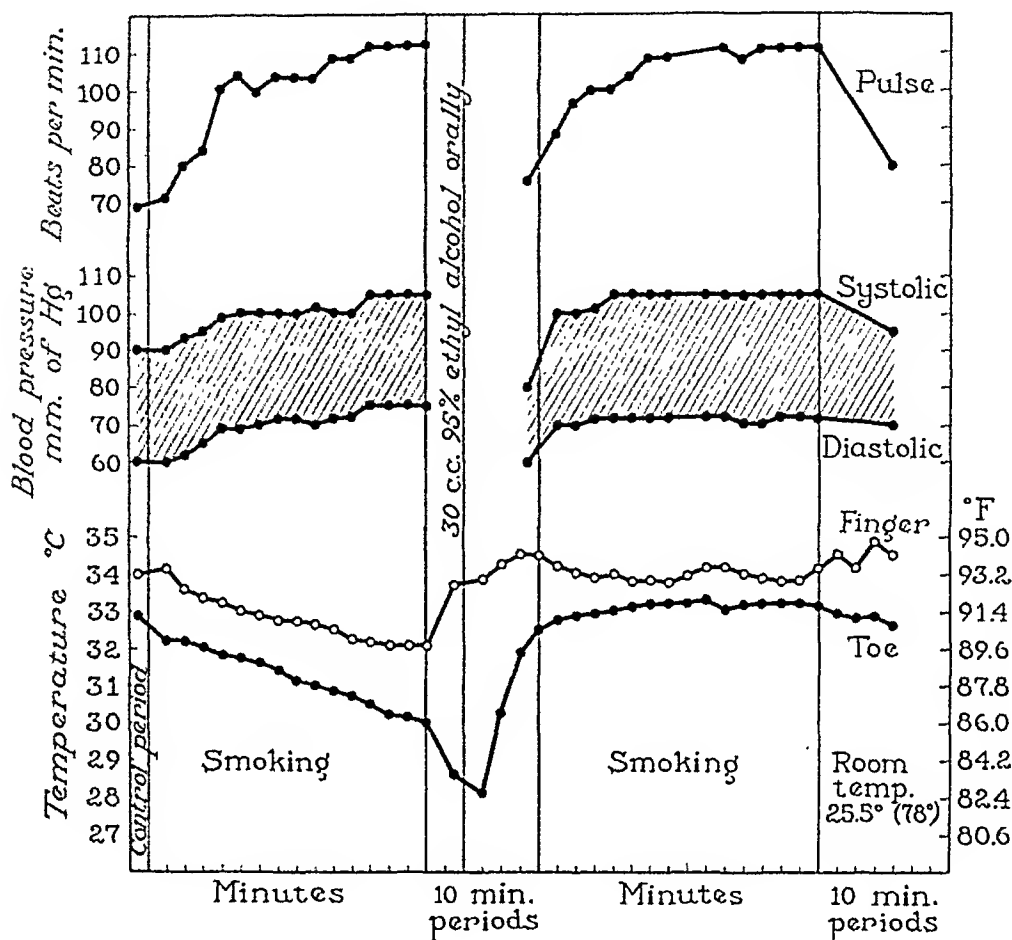


Fig. 1.—The effect of smoking two standard cigarettes, alone and after the ingestion of 95 per cent alcohol, on the skin temperature of the extremities, blood pressure, and pulse rate of the same subject. The skin temperature curves of only one toe and one finger are shown. The control period was sixty minutes. The skin temperature of the fingers and toes failed to decrease on smoking after the ingestion of alcohol. This was an unusual response.

Another subject had evidence of greater vasoconstriction of the blood vessels of the extremities (Fig. 2) than that of the normal subject just mentioned. On smoking before the ingestion of alcohol, the blood pressure and pulse rate of this second person increased definitely. The skin temperature of the toes decreased 5.0° C. and that of the fingers 5.3° C. (Fig. 2). These effects were still evident fifty minutes after the ingestion of alcohol. At that time there was only slight vasodilatation of the toes, for the skin temperature did not approximate the pre-smoking basal level.

On smoking after the taking of alcohol, the skin temperature of the toes of this second subject decreased only 2.5°C . but reached the same level as that which was obtained on smoking before the ingestion of alcohol. The skin temperature of the fingers decreased only 1.5°C . in contrast to 5.3°C . before alcohol. The small decrease of 1.5°C . in the skin temperature of the fingers was the exception instead of the rule, since it occurred in only five subjects of the entire group. The rise in blood pressure and pulse rate was similar to that which occurred following smoking alone.

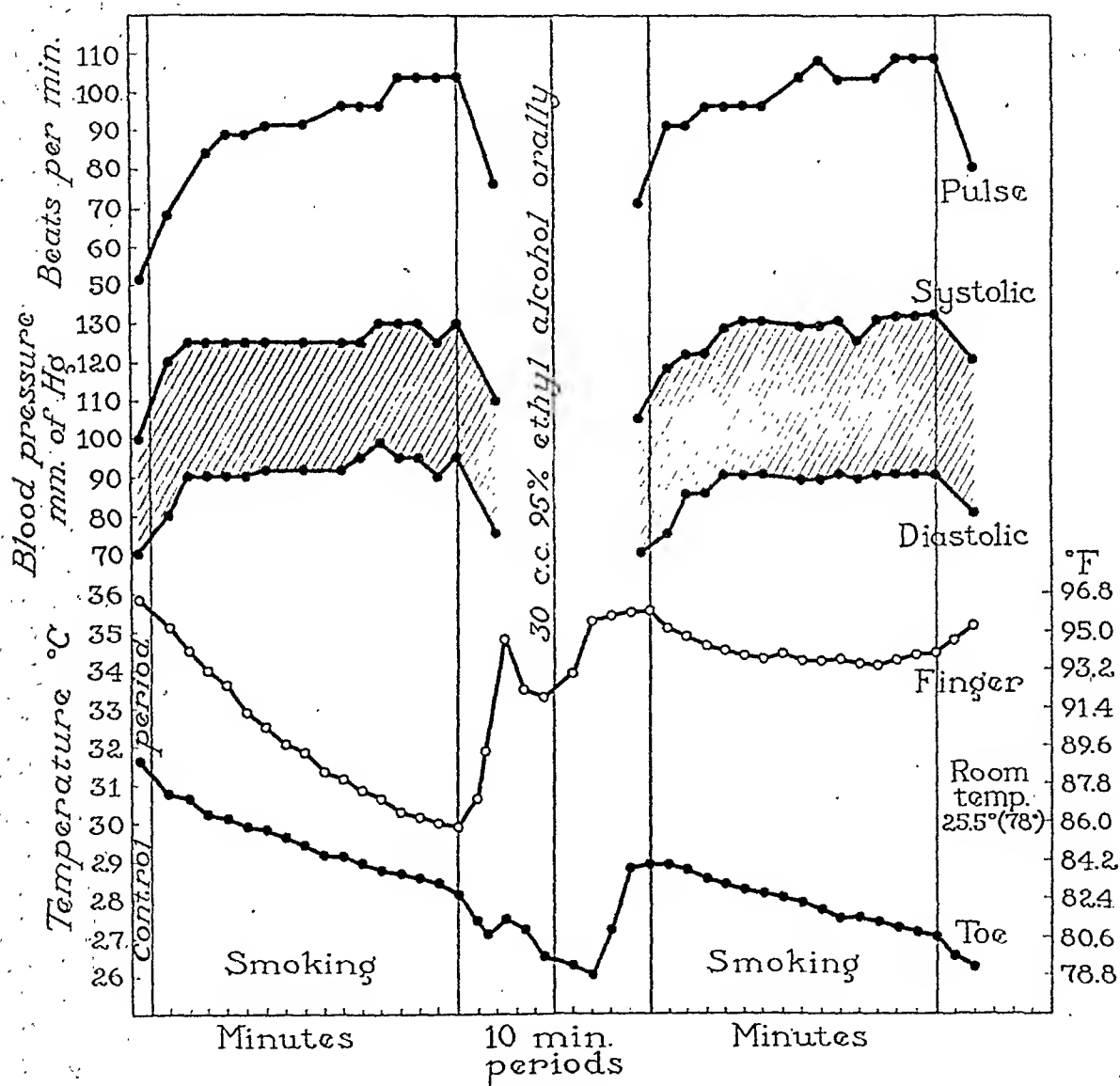


Fig. 2.—The effect of smoking two standard cigarettes, alone and after the ingestion of 95 per cent ethyl alcohol, on the skin temperature of the extremities, blood pressure, and pulse rate of the same subject. The skin temperature of the toes decreased after smoking and failed to return to basal levels in fifty minutes after the ingestion of alcohol.

In many instances the effect of smoking immediately before the ingestion of alcohol persisted and caused us to delay until the following day the test of smoking after ingestion of alcohol.

The more usual effect of smoking after ingestion of alcohol which was experienced by 72 per cent of the subjects tested is demonstrated in Fig. 3. The skin temperature of the toes decreased below the basal level obtained before smoking or the ingestion of alcohol.

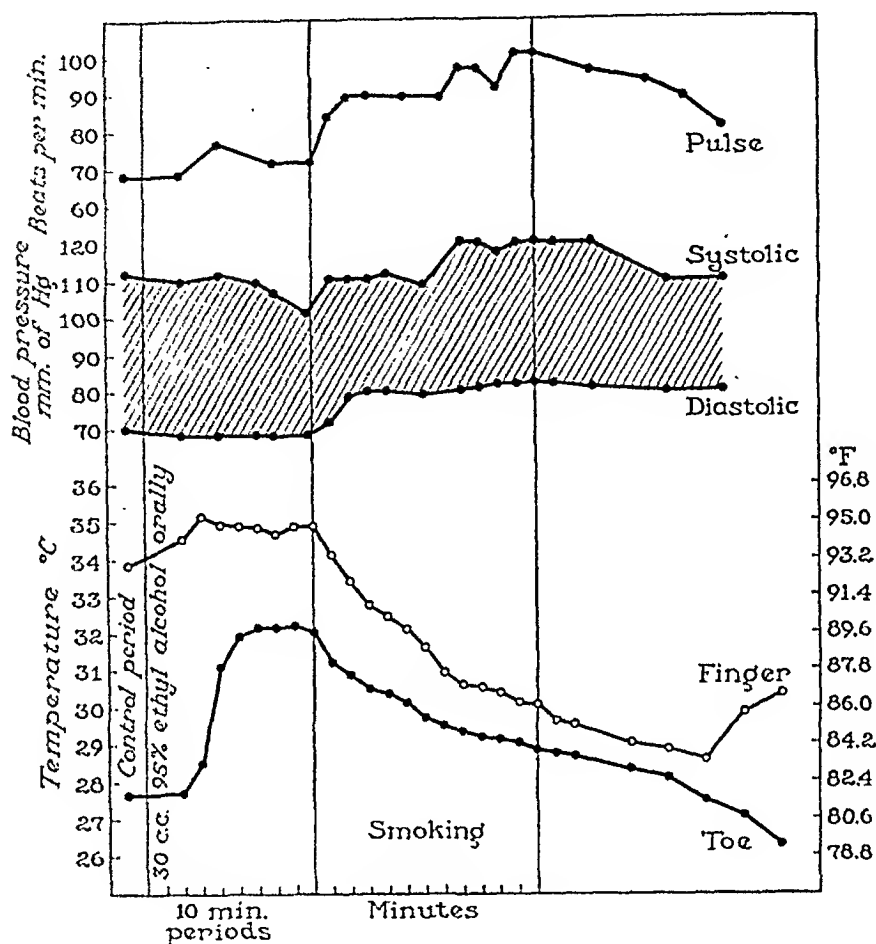


Fig. 3.—The effect of smoking two standard cigarettes after the ingestion of 95 per cent ethyl alcohol on the skin temperature of the extremities, blood pressure, and pulse rate. This was the typical response to smoking.

Results of tests of smoking after the taking of food on two subjects when the control test had been performed the previous day are shown in Fig. 4. The decrease in the skin temperature of the fingers and toes was less in the first individual, whose basal metabolic rate was +1 per cent, than in the second individual, whose basal metabolic rate was -8 per cent. This variation in results shows the correlation of the skin temperature of the toes to the basal metabolic rate. The decrease of the skin temperature of the fingers and toes of the second individual on smoking after the taking of food was similar to that found in many individuals on smoking after ingestion of alcohol. In only four of the tests of smoking after a meal did the skin temperature of the toes remain above the basal

level that existed before eating and that of the fingers remained above the basal level in only two tests. The usual increase of the pulse rate and blood pressure on smoking was noted also on smoking after ingestion of food. This was slightly greater in the second individual, whose test is shown in Fig. 4, than in the first.

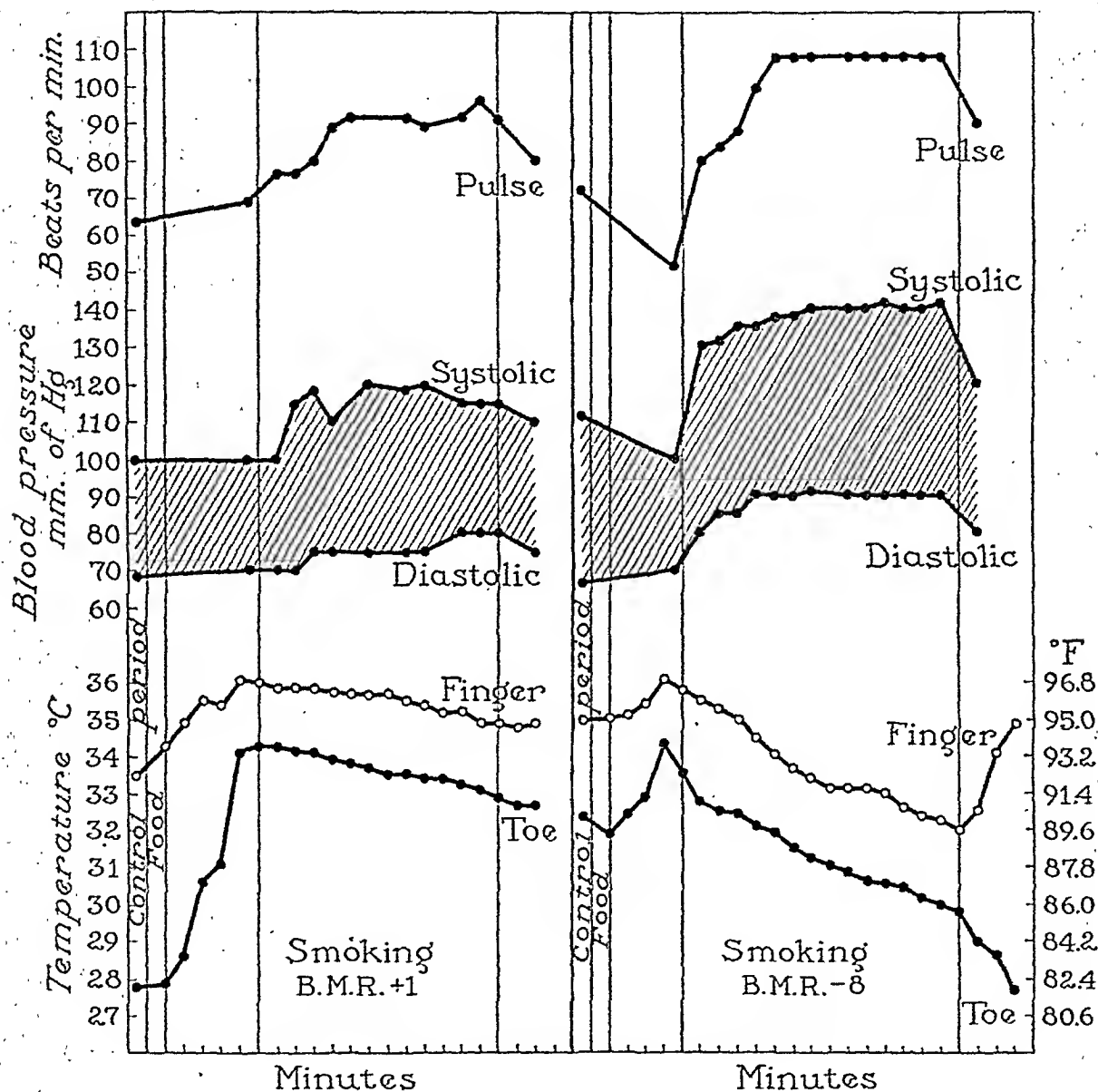


Fig. 4.—The effect of smoking two standard cigarettes after the ingestion of a substantial meal. The difference in behavior of the skin temperature of the fingers and toes with the difference in basal metabolic rate may be noted.

When the physiologic effects of smoking on all subjects were analyzed statistically, the average increase in blood pressure which followed smoking alone was 6 mm. Hg systolic and 5 mm. Hg diastolic more than that which followed smoking after the previous ingestion of alcohol (Fig. 5). When the subjects smoked before the ingestion of food the average systolic pressure was 1.4 mm. lower and the diastolic was 3 mm. higher than when they smoked after the ingestion

of food. These differences, however, could not be considered significant. Likewise, the average differences in the pulse rates on smoking before and after the ingestion of alcohol or food were not significant.

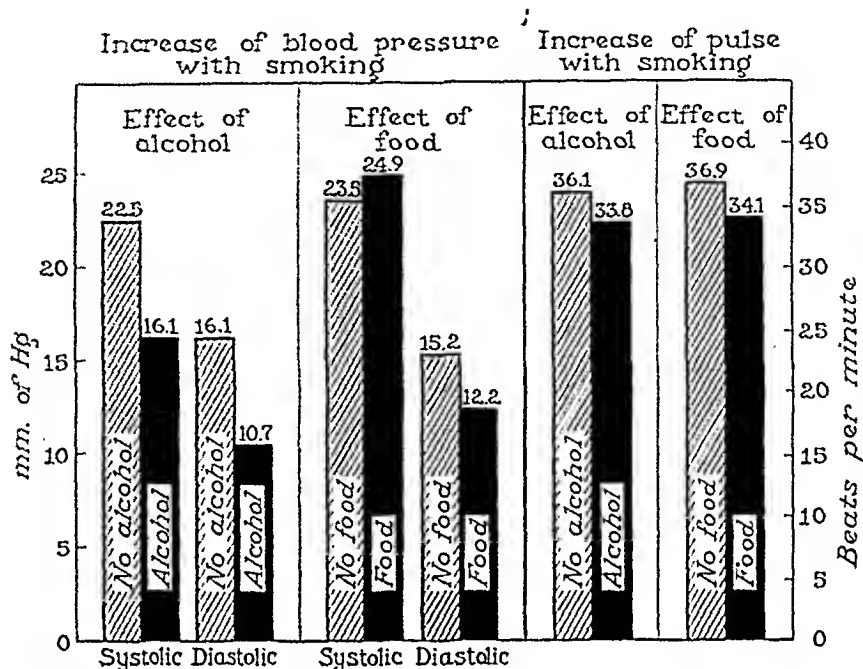


Fig. 5.—The effect of smoking two standard cigarettes on the blood pressure and pulse rate of all subjects before and after the ingestion of alcohol or a substantial meal.

The differences in the average skin temperature of the toes and fingers are shown in Table I. After smoking alone, the average decrease of the skin temperature of the toes in the group in which alcohol was used later was $2.1^{\circ}\text{C}.$, with a range of 0.8 to $5.2^{\circ}\text{C}.$, while the average temperature of the fingers decreased $3.0^{\circ}\text{C}.$, with a range from 0.8 to $6.0^{\circ}\text{C}.$

When the subjects smoked after taking alcohol, the average skin temperature of the toes returned to the basal level and there was a decrease of only $1.3^{\circ}\text{C}.$ in the skin temperature of the fingers. This would seem to indicate that alcohol had prevented the vasoconstriction produced by smoking. However, in 72 per cent of the subjects the skin temperature of the toes was lower than the basal level when smoking was done after ingestion of alcohol. Those who must interpret quantitative results in this field will wish to note the values which indicate definite vasoconstriction as compared with the values at the height of vasodilatation. The decrease shown is of about the same magnitude as that encountered after smoking without the subject's having taken alcohol previously. The same is true for the effects of smoking before and after ingestion of a substantial meal.

TABLE I. MEAN SKIN TEMPERATURE

	DEGREES, CENTIGRADE			
	SMOKING WITHOUT ALCOHOL*		SMOKING WITHOUT FOOD*	
	TOES	FINGERS	TOES	FINGERS
Basal	28.5	33.4	28.5	33.5
Smoking	26.4	30.4	26.5	30.6
Difference	-2.1	-3.0	-2.0	-2.9
	SMOKING AFTER ALCOHOL*		SMOKING AFTER FOOD†	
	TOES	FINGERS	TOES	FINGERS
	TOES	FINGERS	TOES	FINGERS
Basal	28.0	33.4	27.9	32.4
Smoking	28.0	32.1	27.8	31.8
Difference	0.0	-1.3	-0.1	-0.6
At height of vasodilation	30.5‡	34.3‡	29.9§	34.3§
Smoking	28.0	32.1	27.8	31.8
Difference	-2.5	-2.2	-2.1	-2.5

*Probable errors vary from 0.1 to 0.4.

†Probable errors vary from 0.4 to 0.7.

‡From alcohol.

§From food.

COMMENT

The vasodilatation which follows ingestion of alcohol does not take place immediately but only after sufficient absorption of the alcohol has occurred. Therefore, the height of vasodilatation may not be reached until fifty to sixty minutes after the ingestion of alcohol but, once the height has been reached, it persists for one to one and one-half hours. Smoking tests, made at periods varying from thirty to ninety minutes after ingestion of alcohol or ingestion of food, demonstrated that vasoconstriction from smoking could not be prevented by the alcohol or food at any time during vasodilatation from alcohol or food.

The amount of 95 per cent ethyl alcohol used in this study is equivalent to 2 ounces (60 c.c.) of whisky. When either 30 c.c. of 95 per cent ethyl alcohol or 2 ounces of whisky are given after fasting, definite vasodilatation of the peripheral blood vessels occurs. Intoxicating doses of alcohol were not used. It would seem that, under the circumstances of the present study, alcohol is not uniformly an effective agent for the prevention of the vasoconstriction produced by smoking. Therefore, this study does not substantiate the common belief that drinking a cocktail will necessarily nullify the effect of smoking.

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REPORT FROM THE CARDIAC CLINIC OF THE BOSTON LYING-IN HOSPITAL FOR THE FIRST TWENTY-FIVE YEARS

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A CARDIAC clinic at the Boston Lying-in Hospital was started under my direction in 1921. During the twenty-five years, 76,125 women have been treated by the hospital through pregnancy; 1.8 per cent of the total, namely, 1,335, pregnancies occurred in women with heart disease. The maternal death rate for these cardiac patients for the twenty-five years was 3.9 per cent.

Three years after the cardiac clinic started, the maternal death rate for the cardiac patients dropped from nearly 20 per cent to less than 5 per cent. In three-year periods since then, the rate has always been below 5 per cent, and usually less than 3 per cent. The drop in maternal mortality of cardiac patients has been accompanied by a drop in maternal mortality in general. The cardiac mortality, however, dropped suddenly in 1923 when modern methods for the control of our cardiac patients were made effective. Improvement in general maternal mortality has been by lysis and spreads over many years. This drop in the maternal mortality of cardiac patients indicates that for women with chronic rheumatic heart disease, *treatment*, not the vagaries of rheumatic fever, is the largest factor in the prognosis for pregnancy. It supports a belief based on long experience that treatment is the biggest factor in the whole course of young adults with rheumatic heart disease.

For the first fifteen years of the cardiac clinic, the cardiac patients contributed 14 per cent of all maternal deaths; for the last ten years, 28 per cent. *As the general maternal death rate falls, the small number of women with chronic complicating disease becomes relatively more important in determining general maternal mortality.* This fact should be taken into account by those interested in maternal and infant welfare.

The 1,335 pregnant cardiac patients include:

1,244 with chronic rheumatic heart disease	93. %
69 with congenital cardiovascular defects	5.2%
22 with miscellaneous cardiovascular diseases, including cardiovascular syphilis (only 3 cases), thyroid heart, acute pericarditis, etc.	1.8%

One and six-tenths (1.6) per cent of all the pregnancies were in patients with *rheumatic heart disease*. Their maternal death rate was 3.8 per cent.

Those with rheumatic heart disease are subdivided into favorable and unfavorable cases. The definition of a favorable case for pregnancy is a woman with minimal (or more than minimal) signs of rheumatic heart disease who is able to carry on moderate activity without having heart failure and who has no complicating condition which is in itself dangerous, such as essential hypertension, chronic bronchitis, diabetes.

On this basis, the maternal mortality for favorable cases for approximately the first fifteen years at the cardiac clinic was 2.5 per cent. The infant mortality was 12 per cent. For the unfavorable patients, the maternal mortality was 16 per cent and the infant mortality 46 per cent.

During the last ten years, the maternal mortality for the favorable cases has been only 2 per cent and the infant mortality 8.6 per cent. The maternal mortality, however, in the unfavorable cases remains high, namely, 18 per cent; the infant mortality has dropped to 31 per cent.

During the period that these statistics cover, the yearly death rate for women between the ages of 20 and 40 years in the region of Boston was approximately 0.45 per cent. During the last ten years, the yearly death rate for my private women patients between the ages of 20 and 40 years with rheumatic heart disease who were favorable cases by the criteria given was exactly the same as the death rate at the Boston Lying-in Hospital for similar cases in pregnancy. On the other hand, the yearly death rate for my women patients with rheumatic heart disease between the ages of 20 and 40 years who were unfavorable cases was only 6.7 per cent, while the death rate in pregnancy for similar cases at the Boston Lying-in Hospital in the last ten years was 18 per cent. Only twenty-two of those with rheumatic heart disease were found to have *auricular fibrillation* at any time during pregnancy and puerperium; 32 per cent of those with auricular fibrillation died. The infant mortality was approximately 50 per cent. I have found the yearly mortality among comparable nonpregnant women who have auricular fibrillation to be 8 per cent.

A pregnancy, then, has cost the favorable cases little, if any, more risk than their risk of death in one year of living, but it has cost the unfavorable cases a risk nearly three times greater, and those that have auricular fibrillation, a risk that is four times greater.

Individual patients, of course, are more or less favorable and more or less unfavorable. In the Boston Lying-in Hospital cardiac clinic, patients under 23 years of age are, roughly, ten times as liable to recurrences of rheumatic fever as are the older ones. Those who are over 35 years of age are twice as liable to congestive heart failure as are the younger ones. Those with markedly enlarged hearts do not do so well as those that have only slight enlargement. Maternal mortality for those that have mitral stenosis, or aortic regurgitation, or both, is nearly the same, but those who have enlargement of the heart and a systolic murmur (only 6 per cent of those with a diagnosis of rheumatic heart disease) have had a materially lower maternal mortality. Though the maternal mortality is higher for primiparas and those who have had multiple pregnancies than it is for those who are para ii, iii, or iv, these discrepancies can be best accounted for

by factors other than parity; namely, the patient's favorable or unfavorable cardiac status and the patient's age.

It is on these data that we base advice and information given to patients with rheumatic heart disease who are contemplating pregnancy.

The causes of all the maternal deaths among the cardiac patients were:

Congestive heart failure	39%
Bacterial endocarditis	20%
Embolism	15%
Miscellaneous*	26%

The causes of maternal death among favorable cardiac patients were:

Congestive heart failure	12%
Bacterial endocarditis	35%
Embolism	16%
Miscellaneous*	37%

The causes of maternal death among unfavorable cardiac patients were:

Congestive heart failure	64%
Bacterial endocarditis	7%
Embolism	13%
Miscellaneous*	16%

Congestive heart failure caused two-thirds of the deaths among the unfavorable cases, but only 12 per cent of the deaths among the favorable cases. It seems that among cardiac patients, maternal deaths from congestive heart failure would be extremely rare (one in 417 cases) if patients with an unfavorable cardiac status avoided pregnancy. (Many of the patients with an unfavorable cardiac status, however, for one reason or another, desired pregnancy greatly and became pregnant in full knowledge of their danger. It is certainly not to be expected and probably not desirable that all of them avoid pregnancy.)

Among the favorable cardiac patients, 35 per cent of the maternal deaths were attributable to bacterial endocarditis. We hope for fewer deaths from this cause, but there will be more women "cured" of bacterial endocarditis who will later become pregnant and we are not certain of their prognosis for pregnancy.

The maternal mortality of the 69 patients with *congenital cardiovascular defects* was 2.9 per cent.

Patients with *patent ductus arteriosus* (including a few who had had the ductus ligated before pregnancy) have done very well in pregnancy.

There have been no maternal deaths among those with *coarctation of the aorta*, and the infant mortality was satisfactory. Some individuals, however, have had alarming symptoms.

Several of the few with a diagnosis of *ventricular septal defect* have had serious circulatory symptoms after delivery, and there has been one maternal death (another among my private patients).

*Miscellaneous includes deaths from sepsis, "toxemias," hemorrhage, pneumonias, acute appendicitis.

One previously reported patient with the tetralogy of Fallot, severe cyanosis, and drumstick fingers survived six pregnancies with much difficulty, most of this directly after delivery. Only one of the infants survived.

Patients with *essential hypertension* are not analyzed carefully in this report because (1) difficulty in differentiating essential hypertension from hypertension attributable to the "toxemias of pregnancy" and (2) lack of methods for clear subclassification of those that can be confidently diagnosed essential hypertension have prevented the accumulation of large numbers of accurately diagnosed patients. Small numbers of carefully diagnosed patients have been followed. From them we suspect, but cannot prove, that women with mild essential hypertension do as well as the favorable cardiac patients and that those with severe cases do somewhat better than the unfavorable cardiac patients. We suspect, however, though we cannot prove it, that pregnancy tends to hasten the progress of essential hypertension.

In addition to the statistics that the heart clinic has produced in twenty-five years, the following experiences seem to be most noteworthy:

1. The abrupt drop in maternal mortality of the whole group of cardiac patients coincident with the introduction of modern methods for their care (discussed previously).

2. Determination by direct study of the extent of many of the physiologic changes in the circulation attributable to normal pregnancy. The curve of the average load of normal pregnancy on the circulation indicates that the load is small until the sixth calendar month, when it rises steeply to roughly 50 per cent above normal and, on the average, maintains this level until the last calendar month, when it falls off until term. This fall amounts to approximately half the greatest rise. (This is consistent with the fact that congestive heart failure among the cardiac patients is common in the seventh and eighth months and seldom occurs *for the first time* in the ninth month or, indeed, at delivery or afterward.) This lightening of the load in the last month of pregnancy has led to a general principle that patients with severe heart disease, whether they have had or are in congestive failure, are not to be interrupted *for cardiac reasons* after the load on the circulation has once grown heavy (approximately at the sixth month). This is a major change in former obstetric practice. Before the late lightening of the load was determined, it was the custom to deliver patients with severe cardiac difficulty by hysterotomy between the thirty-fourth and the thirty-eighth week of pregnancy, when the child was supposed to be viable, in order to spare the mothers the last of the supposed steadily increasing burden of pregnancy. I believe that the mothers have done better, and certainly the infant mortality has improved, since the present rule was adopted. As a result of this rule, the number of hysterotomies done for cardiac reasons has diminished greatly. Now that interference before term is rare, the cardiac patients are allowed to go into labor and are delivered from below unless there is an indication for hysterotomy that is not related to the heart disease.

Familiarity with the curve of the average load of pregnancy on the circulation is a guide to the cause of failure of a heart. If heart failure occurs before

the heavy rise in the load, or, for the first time, after the load has diminished, normal pregnancy does not account for the failure. There is some complication.

Though there is always a great increase in the load in the last trimester, and always a lightening of the load before term, the load in individuals does not always follow the average curve closely. Some delay the rise into the seventh month; others show the decline before the last month. It is, therefore, impossible to predict accurately how any cardiac patient will behave during pregnancy. It is essential to observe each one closely at frequent intervals. (In the cardiac clinic, patients are examined at least once each week throughout pregnancy.)

NEED FOR CONTINUED STUDY OF THE CIRCULATION IN NORMAL PREGNANCY AND OF SEVERAL NEW CARDIAC PROBLEMS

It is clear from the foregoing statistics that, by modern methods, we cannot expect to make pregnancy much safer for the unfavorable cardiac patients. Their maternal mortality during the last ten years (18 per cent maternal mortality with 64 per cent of the deaths from congestive failure) is even higher than it was ten to twenty-five years ago. The only apparent way to improve this situation is to make pregnancy itself a lighter burden.

Increase in circulating blood volume in normal pregnancy appreciably dilutes the blood. The consequent hurried circulation is not economical. The general edema which is common in pregnancy is sometimes accompanied in normal women by dyspnea and pulmonary edema. The blood dilution and the edema are not well controlled by sodium and fluid restriction, vitamins, and high protein intake; and, so far, our attempts to control the edema by hormone administration have not been successful. It seems that there is some not yet discovered factor that is peculiar to pregnancy. It does not seem unreasonable to hope that this factor can be discovered and controlled if there is vigorous work on the problem. Possibly some of the edema and blood dilution could be controlled by more skillful hormone administration, as is suggested by reports of results from the use of hormones in pregnancy in diabetic patients. Possibly there is a toxin that can be controlled which causes some of the undesirable circulatory changes in pregnancy, as is suggested by the reports of O. Watkins Smith and George Van S. Smith on toxin found in menstrual discharge of women.

A small but important subgroup of women with mitral stenosis can be distinguished. There is little information concerning this group. Without known distinguishing symptoms, they develop sudden, usually apparently unprovoked, severe pulmonary congestion, often with hemoptysis, which often amounts to a hemorrhage. Where there is an apparent provoking cause, the severity of the failure is totally out of proportion to the provocation. Though such symptoms occasionally occur in men with mitral stenosis and in women with mitral stenosis who are not pregnant, and they are rare even in pregnancy, they are much more common in pregnant women than in women who are not pregnant, or in men. These patients cannot be recognized by any method that I know of before pregnancy. Their alarming symptoms may appear early in pregnancy before the

load has grown heavy. So far, those that I have observed have always recovered from their first failure, but in every case they have continued to have recurrences of their violent failure, no matter how carefully the heart failure was treated. Two patients that I know of have died in their second attack. Interruption of pregnancy has *always* been followed by cessation of the attacks or great reduction in their frequency, though they may return months or years later. The pregnancy is a heavy factor in production of the symptoms but the course of the symptoms cannot be explained by any known circulatory phenomena of normal pregnancy. Perhaps the provocation for the attacks is hormonal or toxic disturbance, not yet determined, and peculiar to pregnancy.

Several *new problems of the heart in pregnancy* have appeared in the last few years:

1. Patients with tetralogy of Fallot are extremely rare in a cardiac clinic in a lying-in hospital. The recently introduced successful operation for amelioration of this disease should, in time, bring more cases to obstetric clinics.

2. Subacute bacterial endocarditis, before the introduction of treatment with penicillin, accounted for approximately a third of the maternal deaths in the favorable rheumatic heart disease group. Though a few such patients before the introduction of penicillin treatment bore living children, and a very few cured cases have been reported, all of the women whom I have treated during the last twenty-five years, who were found to have subacute bacterial endocarditis during pregnancy, are dead. Unfortunately, this includes two that have been treated at the Boston Lying-in Hospital since the introduction of penicillin therapy. The infants both died. From questionnaires to obstetricians and cardiologists, reports have been received of seventeen women treated for subacute bacterial endocarditis with penicillin during pregnancy or puerperium. Six of the women died during pregnancy, a maternal mortality of 35 per cent. During the five months following delivery, three more of these women died. This gives a maternal mortality of 53 per cent. The fetal mortality was approximately 24 per cent.

3. Prognosis for future pregnancies for a patient who has recovered from subacute bacterial endocarditis, under penicillin treatment, is an almost completely new problem. Eleven women (two of them in the Boston Lying-in Cardiac Clinic) who have been "cured" of subacute bacterial endocarditis have *all survived* a pregnancy. Three of them were aborted. Six of the eleven had living children. Since such cases are not common, and the need for information on their outcome is apparent, it is suggested and hoped that cardiologists will send information on such cases that they may encounter to the Boston Lying-in Hospital Cardiac Clinic. Information on data thus obtained can be had whenever requested from this clinic.

PHYSIOLOGIC CONDITION OF THE HEART IN THE NATIVES OF HIGH ALTITUDES

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WHEN the physiologic characteristics of those who live in high altitudes are studied, we observe several functional and morphologic variations which distinguish them, without racial considerations, from the normal subject who lives at sea level. The present study was made at 4,540 meters above sea level; the barometric pressure is 446 mm. Hg and the tension of oxygen in the atmospheric air is 80.5 mm. of mercury. The principal physiologic characteristics that have been studied by different authors show the following interesting aspects.

Respiratory Apparatus.—There is a wide thorax with an emphysematous shape and an enlarged lung capacity at the expense of the complementary air and of the residual air.¹ Dissociation curve of hemoglobin deviates toward the right; corresponding to a tendency to acidosis.²

Blood.—The chief findings are polycythemia with more than six or seven million erythrocytes per cubic millimeter; arterial saturation of 81 per cent; 16.5 Gm. of hemoglobin per 100 c.c. of blood; blood volume equal to 120 c.c. per kilogram of body weight with a slight reduction of plasma; more or less pronounced reticulocytosis; and a slight increase in the blood viscosity.

Tissue Respiration.—One of the interesting observations is an increase of the myohemoglobin, especially in the muscles of permanent activity such as the diaphragm and the heart. Since most changes are a manifestation of exaggerated function, it is of interest to determine whether they represent overwork or whether the different organs have acquired a supercapacity, the apparent physiologic effect being a result of a genuine process of adjustment to altitude.

The purpose of this study is to determine the place of the cardiac muscle in relation to this problem. To accomplish this, the data that have been obtained through x-ray, radioscopic, and electrocardiographic studies, and through other means of physiologic investigation, will be analyzed.

FINDINGS

Radiologic Determination of the Size and Shape of the Heart.—The effects of chronic or permanent anoxia upon the heart have been the object of experimental

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studies and of casual and sporadic observations.⁵⁻¹⁰ Investigations based upon x-ray study of the heart were made by us in 1938¹¹ and in 1944 by Miranda and Rotta¹² and by Kerwin.¹³ The data presented in the several published papers have all shown an increase of the cardiac dimensions, but it has not been determined if this increase is contributed by all chambers, or if it is the result of a predominant enlargement of one of the heart cavities. It has not been specified either if the increased size of the heart in man is determined by dilatation or hypertrophy of the heart muscle.

In the present work we have analyzed all the data obtained in 400 telerradiograms of healthy adult subjects who had lived all their lives, or at least for several years, at an altitude of 4,540 meters above sea level. In a group of thirty of them, special examinations were carried out.

In the telerradiograms the transverse diameter and the frontal area of the cardiac silhouette were measured and compared with the normal values for subjects of the same weight and height. The tables and nomograms of Ungerleider and Clark¹⁴ and of Ungerleider and Gubner¹⁵ were used. The results are shown as the percentage of deviation from the normal values, considering as an increase any deviation of more than 10 per cent. For comparative purposes the same determinations were made on teleroentgenograms of more than 200 normal subjects with the same racial characteristics who lived at sea level.

The results demonstrate that the transverse diameter was increased in 69.5 per cent of the cases. The increase was between 11 per cent and 45 per cent, with an average increase of more than 19.5 per cent. In 30.5 per cent of the x-ray films, the transverse diameter was within the normal limits accepted by Ungerleider and Gubner and those found by us in persons living at sea level. The frontal area of the cardiac silhouette, determined by planigraphy, was increased in 67.0 per cent of the cases. The average increase was more than 21.3 per cent, with variations between +11 per cent and +49.0 per cent above the normal values. These figures are greater than those given by Kerwin¹³ who worked at the lesser altitude of 3,600 meters above sea level while we worked at an altitude of 4,540 meters. In Table I we have summarized the results of these determinations.

In 47 per cent of the frontal x-ray films there was definite prominence of the pulmonary conus, and in 25 per cent of the same films there was a well-defined increase of the right lateral border of the cardiac shadow.

In eighty individuals in whom there was an increase of the transverse diameter and of the area of the cardiac silhouette, a radiosopic study of the heart was made, in anterior as well as in right and left anterior oblique positions. In fifty-two of these subjects (65 per cent), well-defined signs of predominance of the right side of the heart were found, such as pronounced anterior arch with a diminished retrosternal space in the right anterior oblique position, disappearance of the normal concavity of the left border, and enlargement of the left side of the silhouette, features that have been pointed out by Schwedel¹⁶ to be manifestations of enlargement of the right cavities. Moreover, in a great percentage of the x-ray films, there could be seen enlargement of the hilar shadows due to congestion of the pulmonary arteries as well as some congestion of the pulmonary vascular network.

TABLE I: VARIATIONS OF TRANSVERSE DIAMETER AND FRONTAL AREA OF HEART IN 400 INDIVIDUALS LIVING AT 4,540 METERS AND 200 INDIVIDUALS LIVING AT 200 METERS ABOVE SEA LEVEL; FIGURES EXPRESSED AS PERCENTAGES OF DEVIATION FROM NORMAL VALUES, CALCULATED ACCORDING TO THE NOMOGRAMS OF UNGERLEIDER AND CLARK¹⁴ AND UNGERLEIDER AND GUBNER¹⁵

PERCENTAGE OF DEVIATION FROM NORMAL VALUES	TRANSVERSE DIAMETER				FRONTAL AREA			
	SEA LEVEL		ALTITUDE		SEA LEVEL		ALTITUDE	
	NUMBER OF CASES	PER CENT	NUMBER OF CASES	PER CENT	NUMBER OF CASES	PER CENT	NUMBER OF CASES	PER CENT
-19 to -15	—	—	—	—	2	1.0	—	—
-14 to -10	2	1.0	—	—	4	2.0	2	0.5
-9 to -5	29	14.5	3	0.75	14	7.0	8	2.0
-4 to 0	61	30.5	10	2.5	43	22.5	21	5.25
+1 to +5	64	32.0	42	10.5	58	29.0	47	11.75
+6 to +10	36	18.0	69	17.25	47	23.5	54	13.5
+11 to +15	7	3.5	90	22.5	18	9.0	82	20.5
+16 to +20	1	0.5	84	21.0	10	5.0	80	20.0
+21 to +25	—	—	54	13.5	4	2.0	41	10.25
+26 to +30	—	—	23	5.7	—	—	27	6.75
+31 to +35	—	—	17	4.25	—	—	22	5.5
+36 to +40	—	—	5	1.25	—	—	8	2.0
+41 to +45	—	—	3	0.75	—	—	6	1.5
+46 to +50	—	—	—	—	—	—	2	0.5

Electrocardiographic Findings.—Since the x-ray and radiosopic examinations showed that many of the subjects who lived in high altitudes had a predominance of the right side of the heart, it was considered desirable to undertake an electrocardiographic study in a group of them for the purpose of obtaining further information. Electrocardiograms were obtained in 100 subjects between the ages of 24 and 58 years. In each subject the three classic leads, six unipolar precordial leads, and three unipolar limb leads were made. For the unipolar leads the central terminal of Wilson, with Goldberger's¹⁷ modification, was used. The electrocardiograms were taken after a rest of ten minutes.

The most essential measurements of the different deflections and time intervals were made, and a three-dimensional study related the results, especially, to the electrocardiographic patterns of right ventricular hypertrophy described by Goldberger,¹⁸ Sodi Pallares,¹⁹ and Myers and Stofer.²⁰ A more complete study with a larger number of subjects is now being made. In the present series the most important results were as follows:

Rate: Monge²¹ has demonstrated by clinical examination that inhabitants of high altitudes often have a slow cardiac rate which may not exceed 35 and 40 beats per minute. In the subjects of our series the recorded beats were between 45 and 84, with an average rate of 66.5 beats per minute.

P Wave: The P wave did not show any important abnormality of duration or amplitude. This wave was often slurred, particularly when the tracings were characteristic of cor pulmonale.

P-R Interval: This interval was within normal limits in relation to the heart rate. The average duration was 0.165 second.

The QRS Complex: The mean manifest axis was determined following the axial system of Sodi, Cuellar, and Cabrera.²² The QRS complex was found to be markedly deviated toward the right (between +90 and +180 degrees) in 59 per cent of the tracings and strongly deviated toward the left (between -90 and -180 degrees) in 21 per cent of the tracings. In the remaining subjects it was found between -10 and +90 degrees. The size of the R and S waves in the classic leads, expressed in millimeters, are given in Table II.

TABLE II.

DEFLECTION	AVERAGE (MM.)	EXTREMES OF AMPLITUDE (MM.)
R ₁	3.35	1.00- 8.50
R ₂	6.00	1.00-15.20
R ₃	5.60	1.00-18.50
S ₁	4.59	0.50-12.00
S ₂	4.65	0.00-12.10
S ₃	2.10	0.00- 8.10

Comparing the maximum and the minimum values with those given by Kossman and Johnston,²³ it can be observed that, as a general rule, R tends to be small and S larger in the first and second derivations, while the opposite occurs in the third derivation. The ventricular complex was classified as being of the S type when this deflection was larger than R in the corresponding lead. In 30 per cent of the series the QRS complexes were of the S₁ type; in 32 per cent, of the S₁ and S₂ type; and in 34 per cent, of the S₁, S₂, and S₃ type. In the precordial leads a positive R (larger than S) was found in V₁ in 30 per cent of the subjects, and in V₁ and V₂ in 6 per cent. The S deflection was larger than R in all the precordial leads when deviation of the axis toward the right or the left was quite accentuated. This configuration was seen particularly in tracings in which the main deflection was negative in the three classic leads. The time of intraventricular conduction was within normal limits in 72 per cent of the cases, the average duration being 0.085 second. In 21 per cent it was between 0.11 and 0.12 second and in seven subjects whose tracings showed the characteristics of right bundle branch block, QRS had a value between 0.12 and 0.14 second.

T Wave: The T wave was inverted or diphasic in Lead III in 55 per cent of the electrocardiograms and in Leads II and III in only four subjects. In the precordial leads, T was negative or diphasic in V₁ in forty-eight subjects; in V₁ and V₂ in eighteen subjects; in V₁, V₂, and V₃ in ten; and in V₁, V₂, V₃, and V₄ in two subjects.

Q-T Interval: The length of this interval was found to be within the normal limits assigned by Ashman and Hull²⁴ in all instances. Electrocardiographic signs of right branch block were observed in 7 per cent of the tracings, and 23

per cent of the records showed the characteristic aspect of right ventricular hypertrophy (cor pulmonale). In twenty-seven individuals the tracings suggested right predominance, even though they did not fulfill the requirements pointed out by Goldberger, by Sodi, and by Myers. It is interesting to note that x-ray examinations were more useful in discovering right ventricular hypertrophy than were electrocardiograms.

Heart Sounds.—In the natives or residents of high altitudes three or even four heart sounds are often heard. These are diagnosed clinically as reduplications of the first and second cardiac sounds. Phonocardiographic study has demonstrated that in most instances these reduplications are real; that is, they are due to the separation of the sound components. The reduplications of the second sound are found associated mainly with radiographic or electrocardiographic signs of predominance of the right side of the heart. The third cardiac sound was often recorded.

Principal Physiologic Aspects of Circulation.—In a group of sixteen subjects selected for their age, ability to cooperate, and prolonged residence at high altitude, the following determinations were made: (1) output per minute; (2) stroke volume; (3) cardiac index; (4) arterial tension; (5) venous pressure; and (6) arm-tongue circulation time (decholin) and arm-lung time (ether). The results were compared with the results of the same determinations made in a group of subjects who lived at sea level. These results have been summarized in Table III.

TABLE III. MAIN CIRCULATORY CHARACTERISTICS DETERMINED IN SIXTEEN NORMAL NATIVE SUBJECTS LIVING AT AN ALTITUDE OF 4,540 METERS, AND IN TWENTY NORMAL NATIVE SUBJECTS LIVING AT SEA LEVEL (LIMA)

	LIMA (SEA LEVEL)		MOROCOCHA (4,540 METERS ALTITUDE)	
	AVERAGE \pm E. P.	EXTREME VALUES	AVERAGE \pm E. P.	EXTREME VALUES
Cardiac output per minute (L./min.)	3.77 0.04	3.29 -4.36	3.81 0.03	3.35 -4.15
Stroke volume (c.c. per contraction)	61.0 1.29	49.0 -85.0	63.0 1.19	52.0 -77.0
Cardiac index (L./M ₂ of body surface)	2.23 0.02	1.95 -2.45	2.42 0.03	3.35 -4.15
Systolic arterial pressure (mm. Hg)	121.0 1.69	109-140	116 1.70	108-126
Diastolic arterial pressure (mm. Hg)	72.3 0.86	60- 85	73 1.00	59 -83
Venous pressure (cm. H ₂ O)	8.4 0.33	6.7 -14.5	9.9 0.24	7.5 -15.5
Arm-tongue circulation time (sec.)	13.4 0.20	10.0 -17.5	16.5 0.55	11.0 -32.0
Arm-lung circulation time (sec.)	5.8 0.22	4.2 -9.0	7.6 0.18	6.0 -10.0

The most important deviations that can be observed in Table III are the following: The systolic arterial pressure tends to low values, as has been proved by Miranda²⁵ in an extensive series of determinations. The diastolic arterial pressure is within normal limits, so that there is a slight decrease of the pulse pressure. The venous pressure is above the limits obtained at sea level with the same methods and by the same observer. The arm-tongue and arm-lung circulation time are slightly prolonged. The cardiac output and stroke volume, respectively, expressed as liters per minute and cubic centimeters per contraction, are within normal limits, but if these data are referred to body surface a slight increase is found. The cardiac output, however, has been determined with the acetylene method of Grollman²⁶ and we have good reason to think that the application of the method, even though corrections be made, is not to be recommended.

DISCUSSION

From these results, it may be concluded that the heart of a man living at high altitudes (4,540 meters) presents a certain degree of globular enlargement, with a predominance of the right side in a good number of cases, as is shown by the x-ray films and electrocardiograms. Since studies of animals living at the same altitude have shown that the cardiac enlargement is due to myocardial hypertrophy,⁶ it is logical to admit that, in man, hypertrophy may be the determining cause of the increased cardiac dimensions. According to the work of Wearn and associates²⁷⁻²⁹ and of Roberts,^{30,31} every hypertrophied heart has an imperfect intrinsic circulation in proportion to its degree of hypertrophy. In the long run, therefore, hypertrophy becomes harmful to the organism. There is nothing at present which demonstrates that the heart at high altitudes does not follow this rule. As to the cause of the hypertrophy, it might be considered a consequence of the "anoxia anoxica" which determines all physiologic changes dependent on altitude. The predominance of the right side which is found in many cases must be related to the pulmonary congestion and other pulmonary modifications which were studied by Hurtado.³² The moderate increase of the venous pressure and the prolongation of the circulation time strengthens the hypothesis of overwork of the right side of the heart. In some subjects this predominance is more evident than in others. While it has not been proved, it is probable that this may be due to a deficiency in the respiratory apparatus more than to alterations of the heart.

SUMMARY AND CONCLUSIONS

Measurements of cardiac size have been verified and a study has been made of some aspects of the circulatory physiology in subjects who are natives living at 4,540 meters above sea level. The determinations include the following: The study of 400 frontal x-ray films in which the transverse diameter and the frontal area of the cardiac silhouette were measured, using the method of Ungerleider and Gubner; eighty fluoroscopic examinations of the heart, especially in the anterior oblique position; analysis of 100 electrocardiograms obtained in the

three classic leads, six unipolar precordial leads, and three unipolar limb leads; and, finally, the study in sixteen subjects of the cardiac output per minute, the stroke volume, the arterial pressure, the venous pressure, and the arm-tongue and arm-lung circulation time.

The analysis of the data obtained gives the following general results:

1. An increase in the transverse diameter of the heart in 69.5 per cent of the cases with an average increase of 19.5 per cent. An increase of the frontal area of the cardiac silhouette in 67 per cent of the subjects with an average increase of more than 21.3 per cent was found.

2. In 65 per cent of eighty fluoroscopic examinations of individuals who showed an increase of their cardiac measurements, clear signs of right heart predominance were found.

3. The electrocardiograms showed the following interesting findings: A_{QRS} was deviated toward the right, between $+90$ and $+180$ degrees, in 59 per cent of the subjects; A_{QRS} was strongly deviated toward the left, between -90 and -180 degrees, in 21 per cent. S was larger than R in all, or in almost all, precordial leads in subjects in whom a high degree of deviation of the axis to one side or to the other existed. The principal deflection was negative in Lead I in 30 per cent of the subjects, negative in Leads I and II in 32 per cent, and negative in the three classic leads in 24 per cent. The intraventricular conduction time was found increased in 28 per cent of the subjects, including seven with right bundle branch block. Tracings typical of cor pulmonale were often observed.

4. Phonocardiographic study demonstrated that the reduplications of the cardiac sounds which have been frequently found in the natives living in high altitudes were reduplications in the strict sense. The reduplications of the first sound accompanied bradycardia, and those of the second sound were associated with radiographic or electrocardiographic manifestations of right predominance.

5. Among the principal circulatory characteristics studied, the most important findings were the following: A slightly high cardiac index; low systolic arterial pressure; normal diastolic arterial pressure, with a decreased pulse pressure; venous pressure higher than that at sea level; and slightly delayed arm-tongue and arm-lung circulation times.

6. All these data suggest that the heart of a native, or of an individual who has lived for a long time at a high altitude, hypertrophies by the effect of "anoxia anoxica." The predominance of the right side, which is found frequently, is due to overwork of this portion of the heart which is the result of functional and anatomic alterations of the lung. At high altitudes the heart is working close to its maximum capacity. A very long stay in high altitudes, therefore, is harmful from a cardiocirculatory point of view.

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STUDIES ON FLUTTER AND FIBRILLATION

II. THE INFLUENCE OF ARTIFICIAL OBSTACLES ON EXPERIMENTAL AURICULAR FLUTTER

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THE circus-movement theory of auricular flutter postulates that in this type of cardiac activity there are one or more impulses which are propagated in one direction around a determined closed path and which recur cyclically and regularly. In the first paper of this series, Wiener and Rosenblueth (1946) showed that for this type of propagation one or more obstacles are necessary, surrounded by conducting tissue. The obstacle should have an effective perimeter sufficiently long to contain the wave represented by the impulse, in order that the front of this wave may always find nonrefractory tissue ahead.

According to the theory, the cyclic frequency of flutter depends on two factors: the conduction velocity of the impulses in the auricular muscle and the effective perimeter of the obstacle around which the impulses circulate. We mean here by "effective perimeter" the length of a string tightly surrounding the single or multiple obstacle. This perimeter is adequate if its length is greater than the product of the conduction velocity of the impulses times the duration of the functional refractory period.

Lewis and collaborators attempted to obtain direct evidence in favor of the circus-movement theory as follows. Lewis, Drury, and Iliescu (1921) showed that in patients with auricular flutter the electrical axis of the P wave rotates 360 degrees during each cycle. Lewis, Feil, and Stroud (1920) studied the long-lasting episodes of experimental flutter which are occasionally seen in dogs after rapid electrical stimulation of the auricle. On the basis of latency measurements, they concluded that this flutter is due to circus-movement of impulses around the orifices of one or both venae cavae or, more exceptionally, around one of the auriculoventricular orifices.

In the present study a more direct test of the theory was attempted by investigating what influence reversible (cocaine) or irreversible (mechanical injury) blocks applied to different regions of the auricle exert on the ease of production of auricular flutter and on its rate.

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METHOD

In dogs anesthetized with dial (0.5 to 0.55 c.c. per kilogram of body weight intraperitoneally), under artificial respiration, the heart was exposed by removal of a portion of the sternum and some of the costal cartilages. In some instances the thoracic sympathetic chains were excised from the stellate to the fourth or fifth ganglion; a later section of the vagi in the neck severed all the nervous connections of the heart.

Two or more pairs of electrodes were fixed on the auricles for stimulation or recording. These electrodes were light steel spring forceps clamped to the auricular wall. The tension on the spring was enough to hold the clamps in place and not strong enough to cause any important damage to the wall. The electrodes were attached to light, flexible, insulated copper wires, which were supported so that they could follow freely the movements of the heart, and did not give rise to recording artifacts of mechanical origin.

The cardiac impulses were amplified through five push-pull stages coupled by capacities and resistances. They were then led to a cathode ray oscillograph where they could be observed or photographed. The electrical stimuli were condenser discharges with frequency controlled by a thyatron; the shocks were sometimes rendered diphasic by means of a transformer. The amplitude of the stimuli was adjusted to two to five times the threshold.

The reversible blocks were obtained by local applications of cotton wicks moistened with a 2.5 to 5 per cent solution of cocaine hydrochloride. Irreversible blocks were produced by crushing the muscle with a dissecting forceps. The injuries could be identified and measured at the end of the experiments by the local extravasation of blood; they did not lead to tearings of the wall.

RESULTS

1. *Criterion Adopted to Determine the Existence of Flutter.*—If flutter is defined in terms of the circus-movement theory of its mechanism, as stated in the introduction, it is clear that it is not possible to affirm its occurrence on the basis of records from one pair of electrodes. The existence of this type of activity can be inferred only from such records. In the description of the experimental results the term flutter will be employed to denote the appearance of impulses with the following characteristics: (1) their pattern differs from that of the normal beats, thus indicating that they were not originated at the pacemaker; (2) their frequency is greater than that of the beats of the pacemaker but does not exceed the limit imposed by the refractory period of auricular muscle when uninfluenced by vagal activity, that is, 8 per second; (3) their rate is slightly accelerated by vagal stimulation or by injection of adrenaline which has an important decelerating or accelerating influence on the rate of the heartbeats; (4) they are rhythmical and their pattern is invariable or recurs with regular cycles. As will be shown in the discussion, these characteristics warrant the inference that this activity corresponds to flutter, as defined by the circus-movement theory.

2. *Flutter in the Normal Auricle.*—In denervated, uninjured auricles only rarely may flutter activity be elicited with the characteristics described. Our observations agree with those of Lewis, Feil, and Stroud (1920). Intense and rapid stimulation of any auricular region for a sufficiently prolonged period usually leads to atypical activity, which outlasts the period of stimulation for some seconds and which is then followed by normal beats (Fig. 1). These after effects of the stimuli, however, do not exhibit the features adopted here to define flutter: the impulses are irregular, arrhythmic, and rapid. This type of auricular response to electric stimulation will be described in more detail and discussed in a subsequent paper.

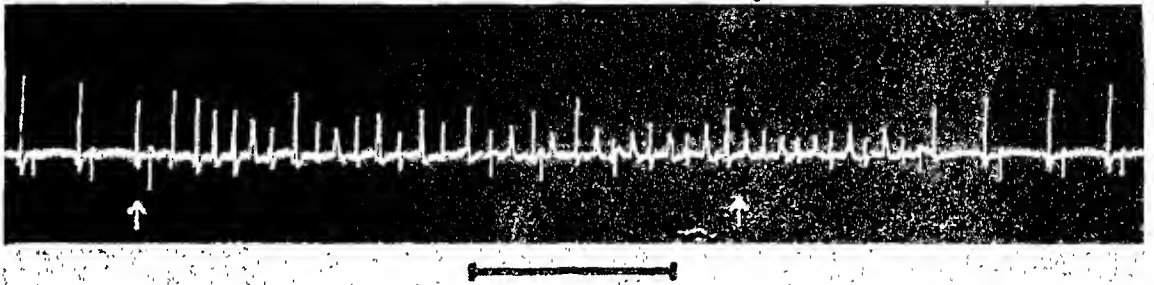


Fig. 1.—Short-lasting series of irregular, relatively fast, impulses that illustrates the typical after-effects of a brief period of strong and rapid stimulation of a normal dog's auricle. Electrical record from two leads on the right appendix. Between the two arrows stimuli were applied at the rate of 50 per second to another pair of electrodes near the superior vena cava. Time calibration, one second.

In exceptional cases, on the other hand, periods of stimulation similar to those described may be followed by relatively slow (6 to 8 per second), regular impulses with all the characteristics of flutter. In their study of experimental auricular flutter, Lewis, Feil, and Stroud used occasional instances of this sort.

The rate of this flutter is in accord with the hypothesis that the effective central obstacle around which the impulses circulate is constituted by the orifices of the two venae cavae. The effective perimeter of these two orifices is approximately 8 centimeters. The conduction velocity of the dog's auricle varies between 40 and 110 cm. per second, according to Lewis, Drury, and Bulger (1921). The theoretic conduction velocity, calculated from the rate of the flutter and the measured perimeter of the assumed obstacle, is from 55 to 65 cm. per second. The theoretic values and the experimental measurements are thus in satisfactory agreement.

If the inference is accepted that the cavae may provide the dual obstacle around which travel the impulses of the experimental flutter in normal auricles, the fact that flutter appears infrequently challenges an explanation. The study of Wiener and Rosenblueth (1946) suggests that the infrequency of occurrence is due to the difficulty of initiating one-way flutter waves around the dual obstacle. Even though a one-way impulse may meet one of the cavae end-on, and thus propagate unidirectionally around it, the presence of a bridge of conducting tissue between the two vessels will usually lead to two-way conduction around the second cava, with a cancellation of the two wave fronts.

This argument led us to expect that a block of the conduction of impulses through the intercaval auricular bridge would ensure the ready and regular appearance of experimental flutter. This expectation was confirmed experimentally.

3. *The Appearance of Flutter After Injuries to the Intervenous Bridge.*—In the eleven dogs studied for this purpose, flutter could be readily elicited after the crushing of the intervenous conducting bridge converted the two cavae into a single obstacle. One or a few periods of intense and rapid stimulation were adequate for the purpose. The rate of the flutter was approximately the same as that measured in the exceptional instances previously cited.

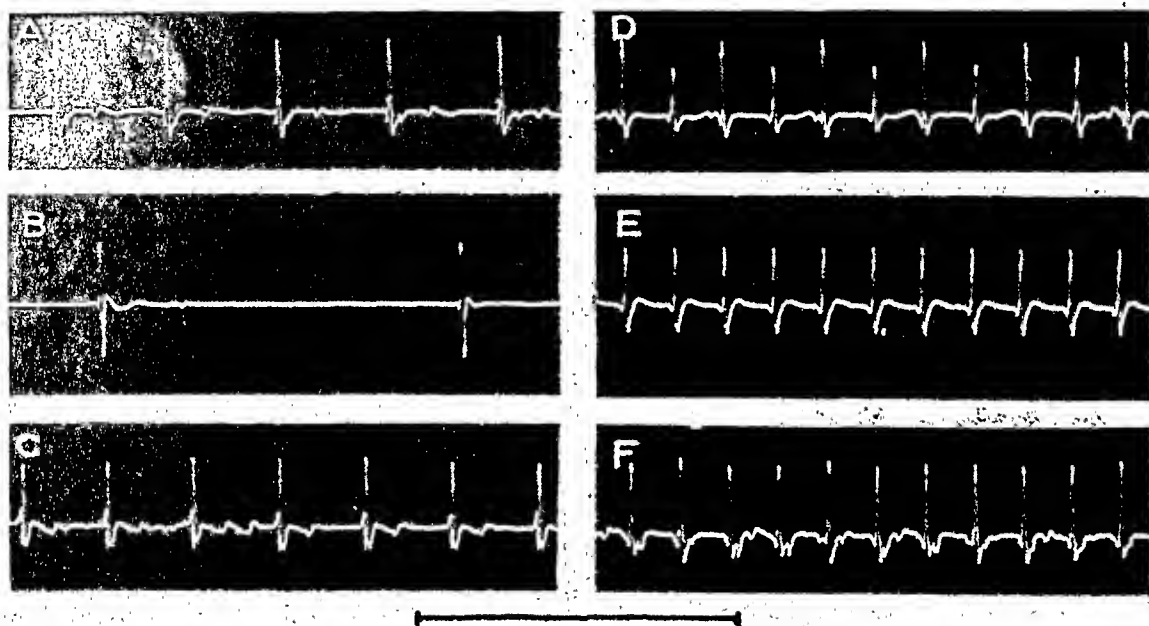


Fig. 2.—Characteristics of the enduring flutter obtained from a brief period of electrical stimulation, after the auricle has been crushed between the two cavae. Recording electrodes placed in front of the superior vena cava. Time calibration, one second.

A, B, and C, Controls before the flutter was elicited. A, Normal beats; B, effects of stimulating the right vagus with a frequency of 12 per second; C, thirty seconds after an injection of adrenaline (20 γ).

D, E, and F, Flutter. D, Alternation of the flutter impulses; E, effects of vagal stimulation as in B; F, effects of an injection of adrenaline as in C.

The rhythmicity and regularity of the flutter impulses is illustrated in Fig. 2, D. Strong stimulation of the right vagus, which slowed the heart beats considerably (Fig. 2, B), slightly accelerated the flutter and eliminated the alternation of responses which had prevailed before the stimulation (Fig. 2, E and D). An injection of adrenaline in a dose sufficient to cause significant acceleration of the beats (Fig. 2, C) modified only slightly the rate of the flutter (Fig. 2, F).

Not only was it easy to initiate enduring flutter episodes after injury to the intervenous region, but it was also quite simple to interrupt a given episode at any time by the application of a few additional electrical stimuli to any region in the auricle. A technique that was effective consistently was the following.

The stimuli were applied with a frequency slower than that corresponding to the flutter. The frequency was then gradually increased until it became slightly higher than that of the flutter. At this stage the stimuli soon gained control of the auricular activity; that is, the oscillograph showed that each stimulus was followed by a response with a fixed latency. If the intensity or the rate of the stimuli was then decreased, it was found that the heart was beating normally.

In some animals, after the initial injury to the intervenous region, a progressive series of additional injuries was made, starting at the lower edge of the orifice of the inferior vena cava and extending the limit of the obstacle toward the auriculoventricular groove. As long as there was a conducting bridge between the obstacle and the ventricle (that is, as long as the obstacle was surrounded by intact auricular tissue), the flutter persisted or could be initiated, but as soon as the injury reached the boundary of the auricle (that is, as soon as the obstacle was no longer entirely surrounded by conducting tissue), the flutter disappeared and could no longer be reinitiated. These observations confirm the inference that the central obstacle for the cyclic propagation of the flutter waves was, in fact, constituted by the orifices of the two cavae.

4. *Reversible Blocks of the Intervenous Region.*—In order to convert the two orifices of the cavae into a single obstacle, it is not indispensable to damage irreversibly the intervenous conducting bridge; a reversible block at this region should be sufficient to permit the initiation of flutter. While ethyl chloride and ether were found ineffective, local applications of a 2.5 to 5 per cent solution of cocaine gave rise, in the majority of the cases tested, to a reversible block adequate for the purpose. The experiment was successful in relatively small dogs (those weighing less than 10 kilograms), while it sometimes failed in larger animals, probably because the external application of the anesthetic does not lead to a block of all the muscular elements at the treated region when the muscular wall is thick.

A typical observation will be described. Strong and rapid stimuli were repeatedly applied through a pair of electrodes attached near the superior cava. The records obtained through another pair of electrodes placed near the inferior cava showed that these stimuli had as aftereffects only the short-lasting, rapid, irregular activity illustrated in Fig. 1 but failed to elicit enduring flutter. A cotton pledget soaked with the cocaine solution was applied for about one minute to the intervenous bridge and was removed. Repetition of the stimulation now gave rise to typical flutter activity, which lasted for one or two minutes. Further renewal of the stimuli failed to evoke flutter unless the intervenous region was again treated with cocaine. Several episodes of flutter could thus be provoked in a given animal by repeated applications of the blocking agent. Unlike the flutter obtained after irreversible mechanical injury, these episodes lasted for only relatively short periods of time and disappeared spontaneously. It is clear that a total block of conduction at the intervenous bridge is a necessary condition not only for the initiation, but also for the endurance of the propagation of flutter waves around the two cavae, when the block is caused by cocaine.

In some animals, after several reversible cocaine blocks had been made and several flutter episodes recorded, the intervenous region was crushed and a new period of long-lasting flutter was initiated and recorded. The rate in all these different episodes of flutter was the same, thus showing that the central obstacle was the same in all cases.

5. *The Influence of the Perimeter of the Artificial Obstacles Upon the Frequency of Flutter.*—In order to test this influence the following observations were carried out. An injury was made at the intervenous region (Fig. 3, 1). Flutter was elicited by appropriate stimulation and its rate was measured. A second

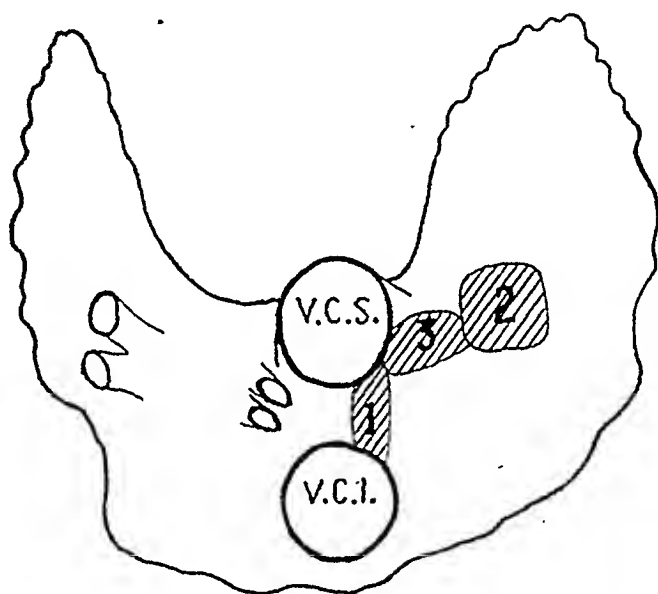


Fig. 3.—Diagram illustrating the method employed to increase the effective perimeter of an obstacle around which circulated a flutter wave. V.C.S., Superior vena cava; V.C.I., inferior vena cava. When the intervenous region was crushed, 1, flutter could be readily elicited. An additional injury, 2, did not modify the rate of this flutter as long as this additional obstacle was not connected with that represented by the two cavae. But when the two obstacles were joined by the crush represented in 3, thus increasing the effective perimeter, the rate of the flutter was significantly decreased.

lesion was then produced (Fig. 3, 2). As long as this lesion was separated from the initial obstacle by conducting tissue, the rate of the flutter was not modified, but as soon as it was connected to that initial obstacle (Fig. 3, 3), the rate of the flutter became significantly slower. Thus, in a typical case, the rate of the flutter after the intervenous region had been crushed was 7.1 per second in several episodes. After the obstacle had been enlarged by the additional injuries, the rate dropped to 6.3 per second. At the end of the experiment the obstacles were measured. The effective perimeter of the first obstacle (the two cavae) was 9.0 cm. and that of the second obstacle (the cavae plus the additional injuries) was 12.7 centimeters. The conduction velocities of the flutter waves, calculated on the basis of the corresponding rates and perimeters, are, respectively, 64 and 80 cm. per second. These theoretical values are in agreement with the experimental measurements of Lewis, Drury, and Bulger which have been

referred to. The fact that the conduction velocity was less when the obstacle was smaller is in accord with the observations of these authors, and our own, that the propagation velocity decreases when the conducting tissue is in the relatively refractory period; that is, as the obstacle decreases in size, the gap between the front and the rear of the flutter wave becomes smaller—the tissue ahead of the front is relatively more refractory.

DISCUSSION

That the activity described here as flutter is due to a circus movement of impulses around an obstacle, or, in other words, that the circus-movement theory of flutter is appropriate, is supported by the following considerations.

1. The regularity of the impulses recorded shows that they reached the recording electrodes through a fixed path. The cases where alternation of responses was present do not vitiate this argument, for it is applicable to every other impulse. Alternation is probably due to the refractoriness of some of the recording elements at the time of arrival of the impulses which gives rise to the smaller electrical deflections.

2. In many animals having an appropriate intervenous lesion, the diphasic records of the impulses in different episodes of flutter, although constant in frequency, could exhibit a reversal of polarity; that is, while in some of the episodes one of the recording electrodes could be first negative and then positive, in other episodes the same electrode could become first positive and then negative with respect to the other lead. The constancy of the frequency is in agreement with the assumption of an obstacle with a constant perimeter; the reversal of polarity is reasonably explained by the assumption that the impulses went around this obstacle in some cases in one direction and in others in the opposite direction.

3. The slight acceleration of the flutter impulses which usually ensued upon stimulation of the vagus reveals a fundamental difference between the normal beats and flutter. The vagus slows the automatic beats of the cardiac nodal tissues. There is no reason, however, for it to slow flutter, since the impulses recorded during this activity are not due to automatic discharges from any region of the heart but are due to the continuously recurring propagation of one or more impulses. Lewis, Drury, and Bulger (1921) have shown that the vagus decreases the refractory period of auricular muscle and that it may increase its conduction rate when this velocity is subnormal because the propagation occurs through relatively refractory tissue. In unpublished observations we have confirmed the data and inferences of Lewis and collaborators. The acceleration of flutter consequent to vagal stimulation is thus readily explained.

4. The slight acceleration of flutter which is obtained by stimulation of the cardiac branches of the sympathetic system or by injections of adrenaline reveals in turn the different nature of flutter as compared to normal beats and can be explained also by an indirect effect on the conduction velocity of auricular muscle via the duration of its refractory period. We have found

(unpublished observations) that adrenaline and sympathin, like acetylcholine, shorten the refractory period.

5. The satisfactory accord between the conduction velocity calculated from the measurements of the rate of flutter and of the effective perimeter of the assumed obstacles and the conduction velocity determined experimentally is direct evidence in favor of the circus-movement theory.

6. Finally, as another datum in direct support of the theory may be adduced the fact that enduring flutter can be initiated only if the assumed obstacle is entirely surrounded by conducting tissue. This datum excludes the possibility of spontaneous beats of ectopic origin.

The preparation described (Result 3) is of obvious importance for the study of flutter. Up to now this study has been handicapped by the rarity of occurrence of long-lasting flutter in normal auricles. Following the simple technique which we have described, flutter episodes may always be readily initiated; they will usually persist indefinitely and can thus be observed at length; they can be extinguished at will, if necessary for the purposes of the experiment.

SUMMARY

In denervated normal dog's auricles, enduring activity with the characteristics of flutter, as defined by the circus-movement theory, can be elicited only rarely by electrical stimuli. If the conduction of impulses through the auricular fibers which lie between the orifices of the two venae cavae is blocked reversibly (cocaine) or irreversibly (crushing), however, activity of this type may be readily evoked and may last as long as the block persists. The importance of this simple preparation for the study of flutter is emphasized.

The activity in question is not initiated at the pacemaker. It is rhythmic and regular (Fig. 2, *D*). Its rate is greater than that of the normal beats (Fig. 2, *D*). This rate is slightly accelerated by vagal stimulations (Fig. 2, *E*) and by injections of adrenaline (Fig. 2, *F*) that have an important typical influence on the rate of the heartbeats (Fig. 2, *B* and *C*). These features are reasonably explained by the circus-movement theory of flutter. In agreement with the theory, additional injuries to the auricle that increase the effective perimeter of the obstacle constituted by the two cavae (Fig. 3) proportionately decrease the rate of flutter. Also in harmony with the theory is the fact that flutter can be obtained only if the obstacle is entirely surrounded by conducting tissue.

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SYNCHRONIZATION OF AURICULAR AND VENTRICULAR BEATS DURING COMPLETE HEART BLOCK

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IN AN experimental work, one of us has shown that, if two isolated frog hearts are placed in contact, there may occur a synchronization of their rhythm (Segers⁵); however, this phenomenon only occurs when the two hearts beat at almost the same rhythm. This proves that interreactions may be developed between neighboring tissues, even when no anatomic connections can be traced between them. It has been shown that such interreactions result from both anatomic and mechanical excitations which are exerted by each of the two hearts on the other.

The existence of interreactions between distinct cellular elements placed in contact with each other is a well-known fact in regard to the nervous tissue. Jasper and Monnier³ have shown, for example, that an excitation can be transmitted from one neurone to another by simple contact. Phenomena of inter-neuronic synchronization have also been observed during rhythmic activity of peripheral nerves and in the central nervous system. In view of these facts, we had wondered whether similar interreactions might not occur between auricles and ventricles in patients presenting complete A-V heart block. We were able to register such a phenomenon in the case which follows.

REPORT OF CASE

V. H., a 77-year-old man, was admitted to the hospital on Jan. 15, 1944. For six months he had been troubled by attacks of dizziness and unconsciousness, especially after exertion. On examination, the pulse was slow, with a rate of about 36 beats per minute. There was an occasional accentuation of the first sound. The roentgenogram showed an increase of all the diameters of the heart. Blood pressure was 220/120.

Electrocardiographic Findings.—Electrocardiograms were recorded daily with the patient at bed rest; they revealed an auriculoventricular block of a very peculiar type. The average duration of the P-P intervals was 0.85 second and that of the R-R intervals exactly twice as long, 1.70 seconds. These intervals changed spontaneously within limits that reached 10 per cent of their average duration. This fluctuation was independent of breathing, and irregular, but the auricular and ventricular rhythms always remained in a 2:1 ratio (Fig. 1). There

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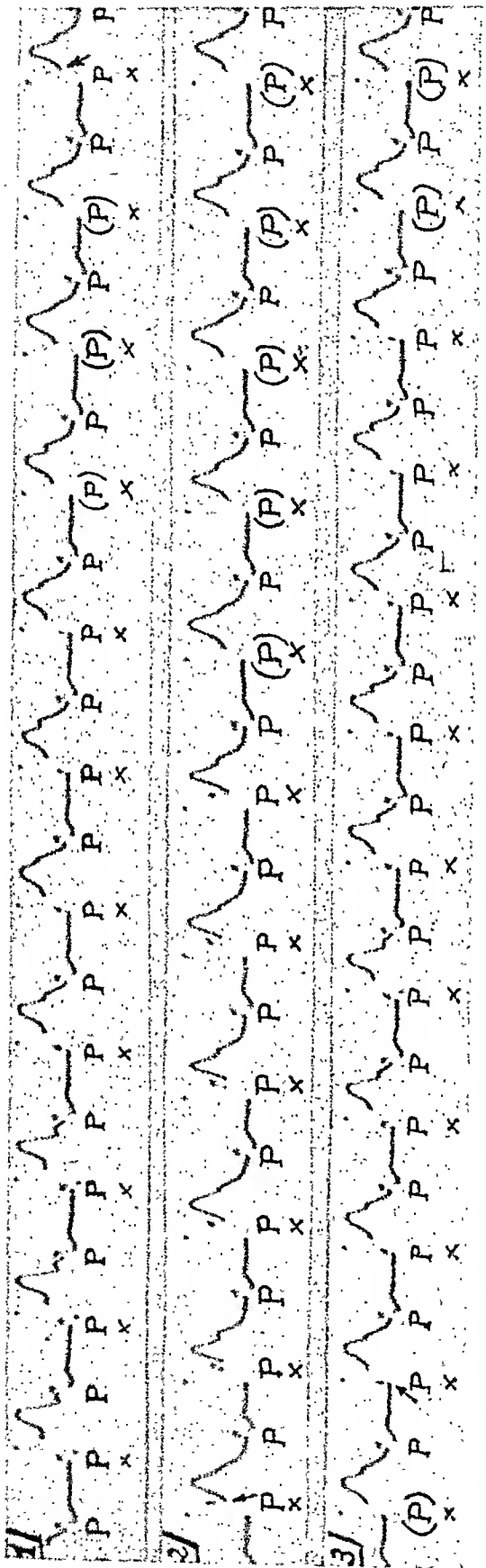


Fig. 1.—Record of complete block with A-V synchronization. Continuous tracing taken with the patient at bed rest (Lead IV R). Every other P wave, marked by a cross, remains in the close neighborhood of R; the 2:1 auriculoventricular synchronization is obvious.

was indeed a close correlation between the activities of the two pacemakers of the heart: in every other auricular cycle, the P wave occurred systematically a little before or a little after the R wave. The respective positions of these two waves were not always the same: according to fluctuations of the rhythm, there was a constant wandering of the P position with respect to R, but the duration of the P-R or R-P interval never exceeded 0.18 second (Figs. 1 and 2). This connection was not fortuitous, for it was recorded daily in this patient, while he was at bed rest, in continuous tracings showing several hundred beats.

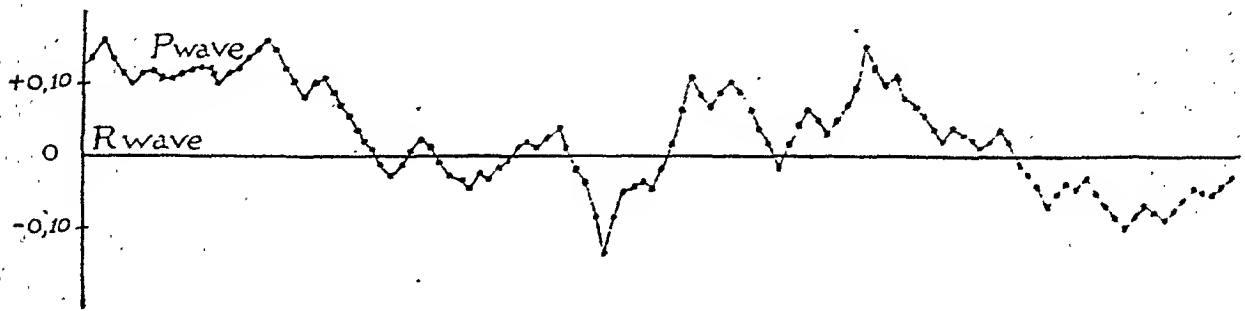


Fig. 2.—Positions of P with respect to R during 121 successive ventricular beats (patient at rest). There is a constant wandering of the position of the P wave with respect to R, but the P-R or R-P interval never exceeds 0.18 second.

The electrocardiograms had two characteristics. Whatever the duration of the recording, the auricular beats were always twice as numerous as the ventricular beats. Although there were slight fluctuations of the rhythm, every other P wave continued to be situated in close proximity to an R wave. However, this was not an incomplete dissociation of a 2:1 type, since the P wave continuously changed its position with respect to the R wave.

An exercise test produced an acceleration only of the auricular rhythm. With the increase in the auricular rate the synchronism of the two pacemakers disappeared (Fig. 4): but a few minutes after the exercise, the auricular rhythm slowed to its former rate and the 2:1 synchronism reappeared. The fact that the auricular frequency could change without influencing either the rhythm or the form of the ventricular complexes shows that complete heart block existed.

Either the 2:1 auriculoventricular synchronism was merely fortuitous, or it was the result of neighborhood interreactions developing between the two pacemakers. The first hypothesis cannot be accepted, for several facts cannot be explained by chance alone. For instance, the fluctuations of the auricular and ventricular rhythms were not absolutely identical, but they did present a correlation, as is proved by the following numerical facts. The duration of two successive P-P intervals varied from 1.53 to 1.84 seconds; the R-R intervals varied from 1.54 to 1.80 seconds. If the two rhythms were independent, there could have been at times a difference of as much as 0.30 second in the duration of the simultaneous P-P-P and R-R intervals; this difference, however, never exceeded 0.10 second. In a more general way, if we measure systematically the difference between the simultaneous P-P-P and R-R intervals, we find a greater number of small values than could be attributed to chance alone (Fig. 3). This correla-

tion between the fluctuations of the two rhythms cannot be attributed to a common vagosympathetic control, since an exercise test produced an acceleration of the auricular rhythm only.

If the auriculoventricular synchronism was merely fortuitous, the P waves could have occupied any position relative to R; the fact is that the P-R or R-P intervals never became longer than 0.18 second at rest. This gives another proof of the correlation between the activities of the auricles and ventricles.

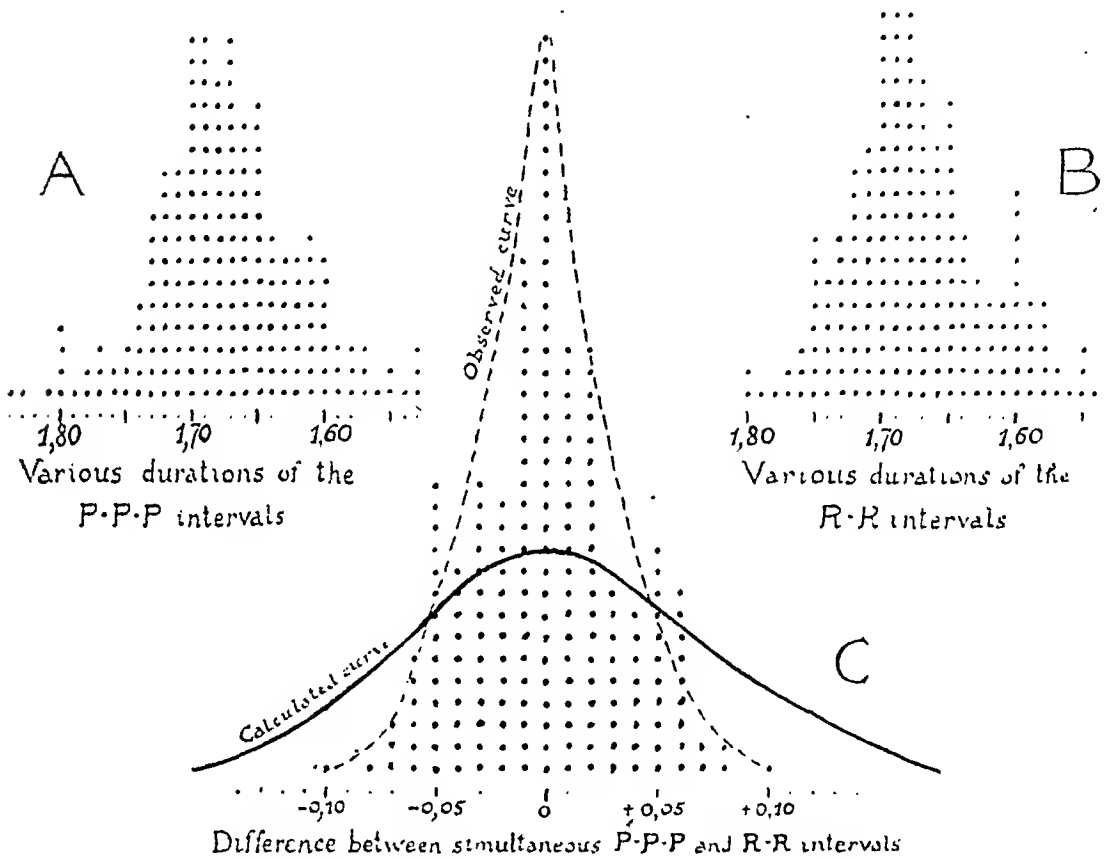


Fig. 3.—Statistical study of the fluctuations of the rhythm observed during 200 successive beats. In A, B, and C the number of dots indicates the number of times each interval was observed. A and B show the frequency of appearance of the several P-P-P and R-R intervals. C concerns the differences in duration between the simultaneous P-P-P and R-R intervals; the observed curve indicates how often the various differences have been noted. The calculated curve shows how often these differences would appear if they were merely fortuitous; the curve is calculated according to the probabilities of combinations between the numerical data of A and B. The number of small values is clearly higher than the calculated one, which implies the existence of a correlation between the fluctuations of the P-P-P and R-R intervals.

As has been stated, after exercise the auricular rhythm was accelerated without a measurable increase of the ventricular rate; but even after exercise, the two pacemakers were not always completely independent. When the increase in the auricular rate was not very much, the P waves did not constantly change their position with respect to the R waves. They did alter their relationship to R rapidly, from beat to beat, when the P waves were relatively far from

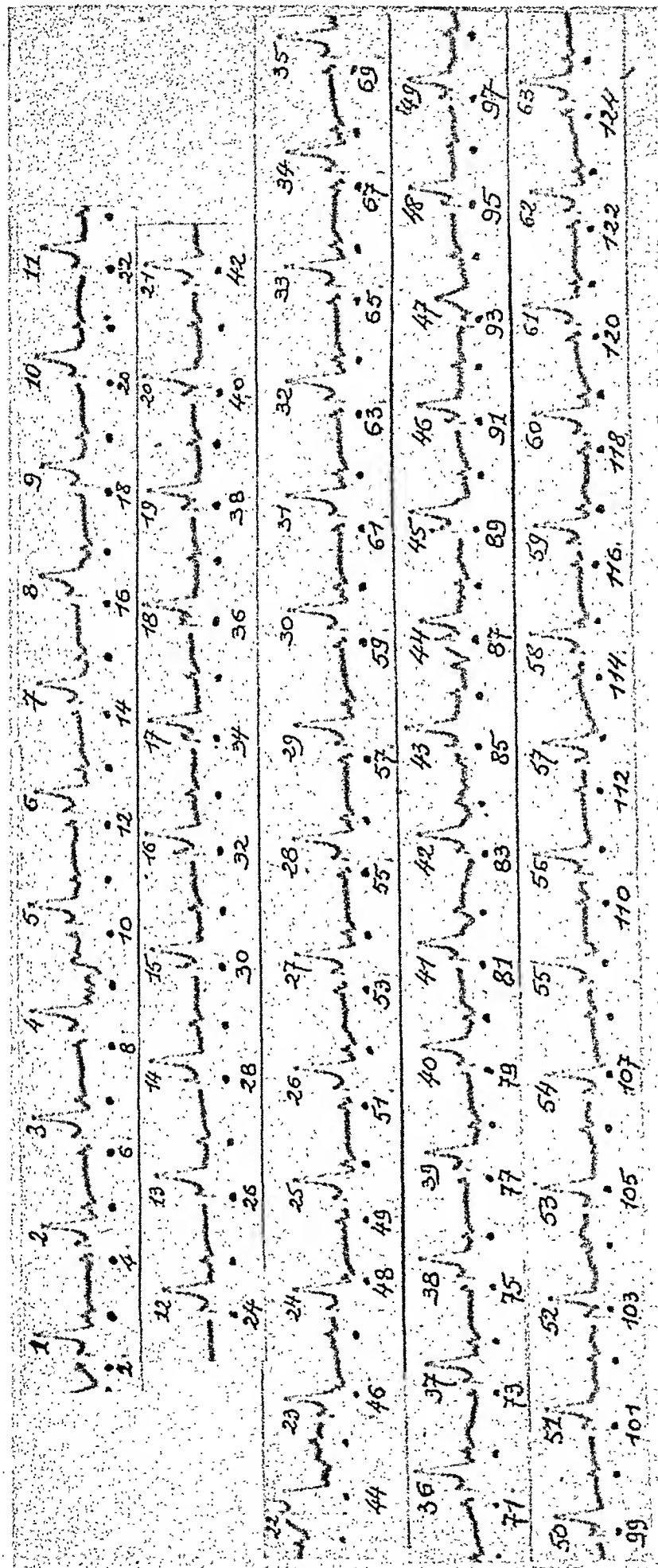


Fig. 4.—Complete block showing the close and dependent association of P and R waves (phénomène d'accrochage). Continuous tracing taken after light exertion. The dots mark the position of the P waves; the auricular and ventricular beats are numbered. The auricular waves indicated by an even number are "hooked" to the R wave during the first twenty ventricular beats. After a rapid change, the P waves marked with an uneven number assume the close association with R waves during the ventricular beats twenty-five to fifty. Then the same sequence of events takes place all over again.

the R waves, but they moved from the R waves slowly when the P-R or R-P intervals were small (Figs. 4 and 5). In other words, whenever the interval between the P and R waves was a small one, these waves had a tendency to remain closely associated or "hooked" together. This phenomenon undoubtedly proves the presence of interreactions between ventricles and auricles which tends to synchronize their rhythms.

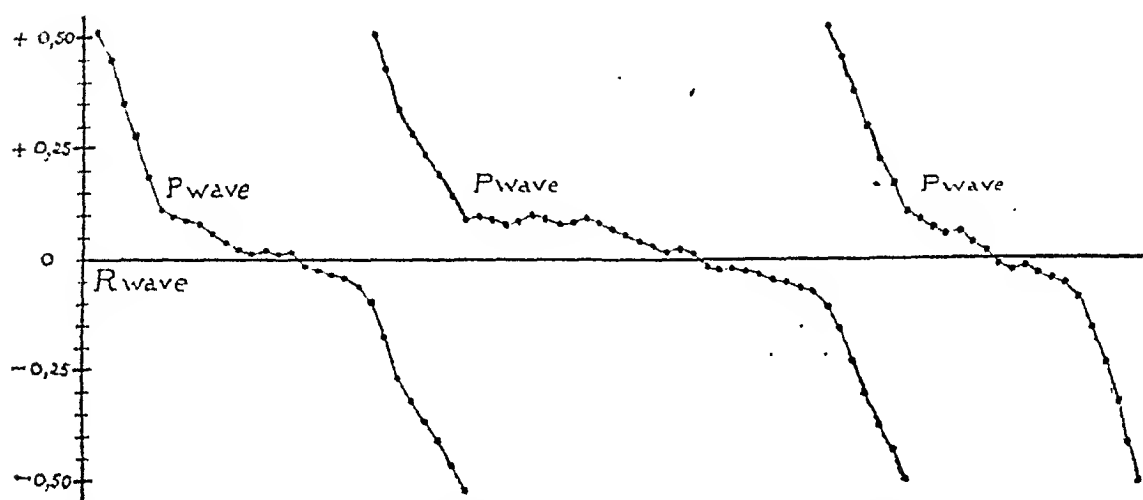


Fig. 5.—Position of P with respect to R during eighty successive ventricular beats (after light exertion). The wandering of P becomes slower in the neighborhood of R.

DISCUSSION

The synchronization of auricular and ventricular rhythms during complete heart block is not a very frequent phenomenon, but when it occurs, it is not due merely to chance. That there exist neighborhood interreactions between auricles and ventricles is shown by the following facts:

1. The auriculoventricular synchronism remains constant even when there are fluctuations of the rate amounting to as much as 10 per cent of the average rate.
2. The P waves remain always in close association with the R waves.
3. Even when the synchronism is abolished by exercise, periodically the P and R waves may assume a close and apparently dependent association (*phénomène d'accrochage*).

The neighborhood interreactions responsible for the synchronization probably result from both mechanical and electrical excitation exerted by the ventricles on the auricles. But the relation so created is by no means as reliable as that normally assured by the bundle of His; indeed, slight exercise is sufficient to destroy the synchronization of the two pacemakers.

Several authors^{2,4,6} have stated that, during complete heart block, the rhythms of the two pacemakers can remain synchronized in a 1:1, 2:1, or 3:1 ratio. The case we have reported demonstrates this fact.

The condition described by French authors as "isorhythmic dissociation" seems to be explained by a similar phenomenon. Of course, in the isorhythmic dissociation, the conduction in the bundle of His is generally not altered, but there exists an autonomous and synchronous activity of auricles and ventricles. This autonomy of the two pacemakers results from the mutual "extinction" of the normal and retrograde impulses in the bundle of His;¹ such a peculiar state can be maintained as long as the two pacemakers beat at the same rhythm. If our interpretation of the isorhythmic dissociation is accepted, the block of the bundle of His should thus not be a necessary condition for the appearance of a synchronization between two distinct pacemakers in the heart.

SUMMARY

During complete heart block, the auricular and ventricular rhythms may in some cases remain synchronized in a 2:1 ratio during very long periods. After exercise, the synchronization disappears, but a close association of a P wave and an R wave (phénomène d'accrochage) may occur. These facts must be attributed to neighborhood interreactions developing between ventricles and auricles, without any conduction pathway. They are similar to the synchronization which is observed when two frog hearts are placed in contact.

We therefore conclude that the rhythms of auricles and ventricles are not necessarily independent during complete heart block.

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COMPARATIVE STUDY OF BLOOD CULTURES MADE FROM ARTERY, VEIN, AND BONE MARROW IN PATIENTS WITH SUBACUTE BACTERIAL ENDOCARDITIS

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BLOOD cultures are of great value in patients with subacute bacterial endocarditis, first, because of their diagnostic importance and, second, because they provide knowledge about the bacteriologic characteristics of the causative organism. In the case of penicillin-sensitive bacteria, this knowledge permits a determination of the sensitivity of the organism to the drug as a preliminary step to prescribing adequate dosage. Disregard of this may lead to undertreatment or to waste of valuable therapeutic material, since the proper dose in cases of *Streptococcus viridans* infection may vary from 100,000 units in infections with relatively sensitive strains to several million units per day in less sensitive strains, such as *Streptococcus fecalis*.

It has been suggested in recent years that arterial blood has a higher bacterial content in patients with septicemia. Murray and Moosnick¹ conducted a comparative study of blood cultures made from the femoral artery and the antecubital vein. In twenty-seven patients studied, fifteen yielded positive cultures: nine of the cultures were positive in the arterial blood only; one was positive in the venous blood only; and five were positive in both arterial and venous blood. Beeson, Brannon, and Warren² found only a very slight difference between the bacterial content of blood from the antecubital vein and the femoral artery; the hepatic and renal veins, however, were notable for their low bacterial content. The only study made with venous and bone marrow blood is that of Barbagallo,³ who found a higher proportion of positive cultures in the latter. In a recent study of patients with brucellosis, the authors⁴ obtained results comparable with those of Barbagallo, the marrow being positive in some instances, when peripheral blood was sterile. This finding prompted us to conduct a similar study in cases of subacute bacterial endocarditis to obtain information about the relative value of venous, arterial, and marrow cultures.

The clinical material consisted of eighty-eight patients, seen at this Institute during the years 1945 and 1946. A set of three cultures (vein, artery, and bone marrow) was taken from the patient as soon as ordered, regardless of the presence or absence of fever. In all, 109 "sets of three" cultures (327 cultures in all) were taken from the eighty-eight patients, several individuals having cultures made more than once.

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The sites for puncture were disinfected with tincture of iodine, ether, and alcohol, and the operator always used sterile rubber gloves. The punctures were made in the antecubital vein, the radial artery, and in the sternal bone at the level of the second intercostal space. In the latter case, to avoid discomfort to the patient, the skin and the periosteal tissues were infiltrated with 2 per cent novocain.

Blood was collected in vials containing enough dried sodium citrate to inhibit blood coagulation. The bone marrow was immediately inoculated into a broth tube, in the ratio of 2 drops per 5 c.c. of media. With citrated blood, poured plates were prepared with melted nutrient agar in the ratio of 1 c.c. of blood to 10 c.c. of media. The remaining blood (5 c.c.) was inoculated in a flask containing 100 c.c. of nutrient broth. None of the media contained clarase or other penicillin inhibitors. All the cultures were incubated aerobically at 37° C. The liquid media cultures were examined microscopically after seventy-two hours and, if found negative, were again examined after seven and ten days. Cultures were considered positive when growth in the liquid cultures was observed which yielded characteristic colonies when planted on solid media. The poured plates were examined after twenty-four, forty-eight, and seventy-two hours, and one week.

Of the 109 "sets of three" cultures (327 cultures in all) referred to previously, only twenty-four (from seventeen patients) gave positive results from one or more of the three sources (artery, vein, and bone marrow). The data are recorded in Table I.

TABLE I. CULTURES OF VENOUS AND ARTERIAL BLOOD AND BONE MARROW FROM PATIENTS WITH SUBACUTE BACTERIAL ENDOCARDITIS (POSITIVE RESULTS)

CASE	ARTERIAL BLOOD	VENOUS BLOOD	BONE MARROW	PENICILLIN TREATMENT
1 (H. I.)	—	—	+	Yes
2 (H. I.)	+	+	—	No
3 (D. M.)	—	—	+	Yes
4 (D. M.)	+	+	—	No
5 (A. C. H.)	—	+	+	Yes
6 (A. C.)	—	+	+	No
7 (A. C. P.)	+	+	+	No
8 (A. A.)	—	—	+	Yes
9 (L. E.)	+	+	+	Yes
10 (L. E.)	—	+	—	Yes
11 (V. C.)	+	+	+	Yes
12 (V. C.)	+	+	+	Yes
13 (V. C.)	+	+	+	Yes
14 (I. L.)	+	—	+	Yes
15 (A. S. A.)	+	+	+	No
16 (E. M.)	—	—	+	No
17 (E. M. N.)	—	+	+	No
18 (M. A.)	+	+	+	No
19 (M. A.)	+	+	+	No
20 (M. A.)	+	+	+	No
21 (S. L.)	+	+	+	No
22 (A. E.)	+	+	+	No
23 (J. S.)	+	+	+	No
24 (L. M. A.)	+	+	+	No

The comparative study of the three different types of culture is shown in the same Table I. Positive results were obtained from arterial blood in fifteen cultures, from venous blood in nineteen cultures, and from bone marrow in twenty-one cultures. *Streptococcus viridans* was the organism isolated in all the cultures. Venous blood was positive in four instances in which arterial blood was negative. In all instances in which arterial blood was positive, venous blood was also positive. In three patients in whom the cultures from bone marrow were negative, positive cultures were obtained from both artery and vein in two patients, and from the vein alone in one patient. Of the five patients whose venous blood was negative, and the bone marrow positive, four were under penicillin treatment.

There was no significant difference in the relative number of colonies observed in poured plates which contained, respectively, arterial and venous blood. The total of the colony countings per milliliter of blood in poured plates containing arterial blood was 541 as compared with 523 in plates containing venous blood (Table II).

TABLE II. NUMBER OF COLONIES FOUND IN POURED PLATES MADE WITH VENOUS AND ARTERIAL BLOOD FROM PATIENTS WITH SUBACUTE BACTERIAL ENDOCARDITIS

CASE	ARTERIAL BLOOD	VENOUS BLOOD
1 (H. I.)	0	0
2 (H. I.)	8	0
3 (D. M.)	0	0
4 (D. M.)	0	0
5 (A. C. H.)	0	22
6 (A. C.)	0	6
7 (A. C. P.)	0	0
8 (A. A.)	0	0
9 (L. E.)	13	7
10 (L. E.)	0	7
11 (V. C.)	20	15
12 (V. C.)	12	14
13 (V. C.)	24	19
14 (I. L.)	0	0
15 (A. S. A.)	17	9
16 (E. M.)	0	0
17 (E. M. N.)	0	0
18 (M. A.)	0	0
19 (M. A.)	0	0
20 (M. A.)	0	0
21 (S. L.)	40	29
22 (A. E.)	209	131
23 (J. S.)	8	39
24 (L. M. A.)	190	225
Total	541	523

SUMMARY

1. A set of three cultures (arterial, venous, and bone marrow) was taken 109 times (a total of 327 cultures) from eighty-eight patients with subacute bacterial endocarditis. Of the 109 sets of cultures, twenty-four were positive in one or more of the three cultures.

2. The incidence of positive cultures was highest in cultures made from bone marrow inoculated into nutrient broth (twenty-one of the twenty-four patients). The incidence was slightly lower in cultures containing venous blood (nineteen of the twenty-four patients). The incidence was lowest in arterial blood cultures (fifteen of the twenty-four patients).

3. Judging from the mean colony counts in poured plates containing arterial and venous blood, there was no obvious advantage of one method over the other.

4. Bone marrow cultures were positive in four of five patients under penicillin treatment.

5. The data emphasize the usefulness of bone marrow cultures in the diagnosis of subacute bacterial endocarditis. It is to be noted, however, that in some instances bone marrow culture was negative when arterial or venous blood cultures were positive.

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Summaries of Other Communications Presented at the Second Inter-American Congress of Cardiology

A number of papers which are presented in abstract form in this issue will be published in full in future issues of the AMERICAN HEART JOURNAL.

THE DIAGNOSTIC VALUE OF ELECTROCARDIOGRAPHIC PATTERNS BASED ON AN ASSAY OF 261 ADDITIONAL AUTOPSIED CASES

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In order to determine the accuracy and dependability of our criteria of electrocardiographic diagnosis, a critical analytic study was made on a series of patients with autopsy control. The necropsy files for a period of five years (May, 1940, to May, 1945) were examined and those cases who had come to necropsy within two months after having an electrocardiogram were selected for study. Two hundred sixty-one consecutive cases were thus studied. The electrocardiograms on each patient were interpreted without consulting the anatomic data, and then the interpretations correlated with the necropsy findings. The accuracy of our interpretations was assayed, and all cases in which a discrepancy existed between the electrocardiographic diagnosis and the necropsy data were studied in detail. Thirteen specific electrocardiographic patterns were separated, as well as nonspecific electrocardiographic abnormalities, and normal records. Forty-one (15.7 per cent) of our cases constituted discrepancies, the remaining 220 (84.3 per cent) showing agreement between the electrocardiographic findings and the pathologic data.

In general, the electrocardiogram was found to be a good index of anatomic normality and abnormality of the heart, although its use is limited by its inability in many cases to distinguish clinical from subclinical forms of heart disease. Occasionally, a normal electrocardiogram may be found with anatomic heart disease, and therefore a normal electrocardiogram cannot be considered to rule out heart disease. A definitely abnormal electrocardiogram, on the other hand, is excellent evidence for anatomic abnormality of the heart.

Ventricular hypertrophy is usually reflected in the electrocardiogram by patterns of heart strain. However, ventricular hypertrophy may, on occasion, be present without electrocardiographic evidence of heart strain, and conversely, other changes may mimic the pattern of heart strain. For example, left heart strain may be imitated by an old anterior wall infarction. With the use of multiple chest leads, left ventricular hypertrophy more often gives rise to a characteristic strain pattern than does right ventricular hypertrophy. With combined ventricular hypertrophy the patterns of the predominantly hypertrophic ventricle are seen more often than a pattern diagnostic of combined heart strain.

Recent myocardial infarctions of any variety, especially if serial records are available, are seldom missed electrocardiographically, although old infarctions or severe coronary arteriosclerosis without confluent infarction may give rise to patterns indistinguishable from recent infarctions, presumably because of coronary insufficiency. Old, healed myocardial infarctions can often be diagnosed electrocardiographically but not with the regularity of recent infarctions. Often a healed infarction leaves as its only electrocardiographic residue nonspecific abnormalities. As with recent infarctions, old infarction patterns may be mimicked by other conditions. Coronary arteriosclerosis without confluent infarctions generally resulted in nonspecific electrocardiographic abnormalities.

The patterns described for congenital heart disease were diagnostic in this series, although the pattern of Katz and Wachtel may be mimicked on occasion in the adult by other conditions. The patterns of uremia, of acute diffuse pericarditis with or without concomitant myocardial infarction, and of acute and chronic cor pulmonale were all diagnostic when encountered, but the electrocardiographic pattern is not invariably present in these conditions. A pattern similar to a recent posterior wall infarction may be seen in acute cor pulmonale.

Mitral P wave was in this series diagnostic of severe rheumatic mitral disease, and P pulmonale was in every case associated with either chronic cor pulmonale or chronic pulmonary pathology (emphysema in all cases), except in one case of congenital heart disease in which it accompanied right auricular involvement. Anatomic chronic cor pulmonale may exist in the absence of a P pulmonale.

A variety of miscellaneous cardiac abnormalities gave rise to nonspecific electrocardiographic changes.

The results in this study definitely indicate that the recognition of specific electrocardiographic patterns greatly enhances the diagnostic usefulness of the electrocardiogram.

CHRONIC HEART INVOLVEMENT IN CHAGAS' DISEASE

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The authors point out that an increasing interest in Chagas' disease has led to the recognition of a considerable number of cases that have cardiac involvement. Complement fixation tests, done routinely in a general hospital, show a 4 per cent incidence. This suggests that many cases formerly diagnosed chronic myocarditis might have been more properly diagnosed "trypanosome involvement of the heart." Of the twelve cases studied, ten of the patients lived in shacks where triatomideos (bedbugs) which are known vectors, were found. In all patients the disease began insiduously and presented the picture of a chronic illness; in none was the picture that of an acute illness. The authors consider that profound weakness is the most striking symptom. Syncope was commonly encountered and occasionally gave the first clue to the diagnosis. In some instances this symptom was undoubtedly due to complete auriculoventricular dissociation. Palpitation was noted as well as bradycardia and weak pulse. All patients had congestive heart failure. Not uncommonly the congestive failure was progressive and ended in sudden death. Of six patients who died, only one had symptoms for four years, the others had had symptoms for less than one year. One of these had been ill but one month and died suddenly after treatment with digitalis.

Teleroentgenograms showed dilatation of the heart in all cases. Pulsations of the heart were of small amplitude. Electrocardiograms frequently revealed changes in conduction. In two instances auriculoventricular block was present. Various degrees of intraventricular block were present. In two instances there was definite right bundle branch block. This latter finding has been reported by others and is considered one of the peculiarities of the disease.

Histologic changes consisted of degeneration of the myocardial fibers due to multiplication of the parasites within the heart muscle, with focal or diffuse inflammatory reactions near the vessels. Isolated nests of parasites were noted and in three cases were found deep between muscle fibers. The authors noted diffuse edema of a degree sufficient to "dissociate the walls of vessels."

COMPARATIVE STUDY OF DIFFERENT PRECORDIAL LEADS

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1. Each kind of precordial lead (from CR₁ to CR₆, from CL₁ to CL₆, from CF₁ to CF₆, from V₁ to V₆) was recorded in ten normal controls. A comparison was then made of the findings in precordial leads recorded by using Wilson's central terminal (Leads V₁ to V₆) and the ordinary types of precordial leads (CR₁ to CR₆, CL₁ to CL₆, CF₁ to CF₆) in about one hundred patients with heart disease. These were selected to include the following conditions: left or right axis deviation, ventricular hypertrophy, angina pectoris, coronary sclerosis, and myocardial infarction.

2. The different precordial leads recorded in normal persons with the precordial electrode in the same place were very much alike; there was no important change when the indifferent electrode was moved from the right arm to the left arm, to the left leg, or united to the Wilson's terminal. There were significant variations with the changes in the position of the precordial electrode, but the findings recorded at Positions 1 through 6 were very similar in the CR, CL, CF, and V leads. As the electrode was moved from right to left (from Position 1 to Positions 5 or 6) R gradually increased and S decreased. A downward or negative T was not found normally in precordial leads, except in those taken with the precordial electrode at the right margin of the sternum. A downward or negative P was often found in Leads CF₁ to CF₃ or CF₄.

3. In cases of ventricular hypertrophy a wider QRS complex in precordial leads and a positive shift of the S-T segment in tracings made at Positions 1 to 4 was found both in leads using the Wilson terminal and in the CR leads. The R wave was of higher amplitude in Leads V₅ or CR₅ in patients with left ventricular preponderance and in Leads V₁ or CR₁ in patients with right ventricular preponderance.

4. In patients with angina pectoris or with coronary sclerosis no significant change was found in precordial leads. In both V and CR leads, however, there was a slight shift of the S-T segment upward in tracings made from Positions 1 to 3, and downward in tracings taken from Positions 5 and 6.

5. A downward or negative T wave was found to be a more constant and important change in the electrocardiogram in patients with old myocardial infarction. A downward T in the third standard limb lead and an upward T in precordial leads was found in posterior myocardial infarction, using the V, the CR, or the CF leads. A downward T in precordial leads in anterior and lateral myocardial infarction was found using the V, the CR, or the CF leads. There was no important influence of the place of the distant electrode or of the terminal of Wilson in the changes in Q and R waves provoked by myocardial infarction in the patients studied.

6. Since no important variation was found in normal nor in abnormal conditions in the precordial leads using the CR or the V leads, we think there is no practical advantage in preferring the latter. CR leads are easier to be recorded. Since in some normals a downward P and a downward T was found in Leads CF₁ to CF₃, we regard CR leads as preferable.

COMPARATIVE STUDIES WITH THE THREE TYPES OF ELECTROCARDIOGRAPHIC LEADS (CLASSIC, UNIPOLAR EXTREMITY LEADS, AND MULTIPLE PRECORDIAL LEADS) IN RELATION TO CLINICAL AND RADIOLOGIC EXAMINATIONS

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For the purpose of investigating which of the three types of electrocardiographic leads give better indications of changes occurring in the cardiocirculatory system, the authors studied 375 patients from the clinical, radiologic, and electrocardiographic standpoints.

The 375 patients were classified as follows: 121 showed no evidence of abnormality of the cardiocirculatory system by clinical, radiologic, and electrocardiographic study; 187 had hypertension; 23 gave a history of angina pectoris; 18 had valvular lesions; 10 had some type of congenital heart disease; and 16 patients had myocardial infarction.

Electrocardiographic studies were made with a string galvanometer. Unipolar leads of the limbs were taken with Goldberger's modification of Wilson's central terminal method.

The conclusion of the authors is that no single type of lead is to be preferred, since all three types of leads give valuable information. Precordial leads were superior to other leads in studying infarction of the anterior wall and bundle branch block. Classic and unipolar leads of the extremities gave the same results; the latter proved to be more useful because they were unipolar.

AN EASY METHOD FOR CALCULATING THE VALUE OF THE MEDIUM AXIS AND THE VENTRICULAR GRADIENT

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1. The author proposes a very simple method for measuring the manifest mean electrical axis of QRS and the manifest ventricular gradient both in their direction and their magnitudes. The direction of the vectors can be found by means of charts like that of Dieuaide or that of Carter and Richter. But the angle *alpha* that the vectors form with the horizontal can be found also by the following formula which the author proposes:

$$T \text{ angle } \alpha = 1.155 \frac{e_3}{e_1} \text{ plus } 0.577$$

in which e_1 and e_3 are, respectively, the projected areas in Lead I and Lead III. With the aid of the slide rule the calculation of the direction of the desired vectors becomes an easy task.

2. The measurement of the ventricular gradient can be made by multiplying the net area of the QRST complex in Lead I by the secant of the angle *alpha* made by the vector with the horizontal.

3. The method of Ashman and the geometric procedure are described for comparison. Examples are given.

SELECTIVE PLACEMENT OF PATIENTS WITH HEART DISEASE IN COMPETITIVE EMPLOYMENT

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A plan of selective placement of patients with heart disease in employment which their limited cardiac reserve will permit them to accomplish safely is presented. It requires close cooperation of the cardiac clinic with the employment service. There are three basic parts to the plan: the physical capacities appraisal of the patient, the physical demands analysis of the job, and the matching of the former against the latter when placing the patient in a job. For successful accomplishment the plan requires the participation of three specialists: the cardiologist, the job analyst, and the employment placement officer.

A special unit of the New York University Cardiac Clinic of Bellevue Hospital is utilizing such a plan in cooperation with the United States Employment Service. Known as the Work Classification Unit, it is also attempting to gather data on the effect of occupation on the course of heart diseases.

CARDIAC NEUROSIS

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The cardiologist must treat in his office, not only patients having organic heart diseases, but also patients having no cardiocirculatory abnormalities. The latter constitute some 50 per cent of all persons consulting the specialist. These patients with symptoms but without organic disease can be divided into at least three groups:

1. Patients with cardiac phobia. The patient's difficulties are the result of exaggerated apprehension, of autosuggestion, or of hypochondriasis.

2. Patients with false heart disease. The physician's oversolicitous attitude or a too-thorough heart examination sometimes focuses and fixes the patient's attention upon a given symptom which in itself is of no significance. Unfortunately, the physician is sometimes responsible. All too often the improper interpretation of an unimportant auscultatory sign, the use of improper technique in taking the blood pressure, or a wrong interpretation of an electrocardiogram which is within the physiologic pattern may lead to a diagnosis of cardiovascular disease when no disease exists.

3. Patients with hyperactive cardiac reflexes who present transitory symptoms of abnormal function of the heart without organic lesion. Some of the conditions that these patients show include neurocirculatory asthenia, paroxysmal tachycardia, transitory bradycardia, hyperexcitability of the carotid sinus, and an exaggerated gastrocoronary reflex (Roemheld syndrome) caused by gaseous distention of the stomach.

To these three groups must be added those patients who develop neurosis and even psychosis as a result of arterial hypertension.

A REVIEW OF EIGHT CASES OF WOLFF-PARKINSON-WHITE SYNDROME INCLUDING FOUR CASES WITH INITIAL LEFT VENTRICULAR ACTIVATION AS DEMONSTRATED BY THE MULTIPLE PRECORDIAL LEADS

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From 6,900 patients examined by the electrocardiograph at the U. S. Naval Hospital, Long Beach, Calif., eight cases of Wolff-Parkinson-White syndrome, characterized by the short P-R interval and the wide QRS complex, were found.

The present consensus of opinion concerning the mechanism of the conduction pattern points to the presence of an anomalous muscle bundle or bundles which connect the right atrium and right ventricle, thereby providing an accessory pathway for the excitation wave. Wood, Wolferth, and Geckler have described such a pathway on the right side of the heart which was present in a patient with this syndrome. The suggestion has been made that this connection may be similar or identical to the "right lateral bundle" as described by Kent many years ago.

If the accessory muscle bundle is the mechanism for this syndrome, the patterns of the precordial leads in the present series suggest that this bundle is not restricted to the right heart. An analysis of the precordial leads in the present eight cases indicates that in four of the patients the left ventricle was activated before the right ventricle. These four showed QRS complexes of the M shape in leads over the right side of the heart, similar to the pattern seen in right bundle branch block; the remaining four had W shaped complexes in leads from the same area, similar to that seen in left bundle branch block. In the former, it is noted that there is an initial positive deflection, which is broad at its base, in leads over the right side of the heart; and in the latter it is noted that the same initial positive deflection occurred in leads over the left side of the heart. This characteristic slurring is uncommon in cases of bundle branch block.

Three patients, two of whom were past the age of 50 years, presented definite evidence of organic heart disease. The remaining five patients revealed no apparent heart disease. Four patients had no cardiac complaints. Only two complained of palpitation or of symptoms suggesting paroxysmal tachycardia.

ALTERATIONS IN THE STRUCTURE OF THE LIVER CELL IN CONGESTIVE HEART FAILURE

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Depolarization of the liver cell (Minkowski), which causes jaundice in hepatic cirrhosis, has a specific histologic appearance which we have called "cholechrysocytosis." It is regarded as the specific morphologic basis of "regurgitational" jaundice in hepatic cirrhosis. Its origin is explained as follows: The cells of the bile ducts have the function of regenerating those parenchymatous elements which are lost during the disease. As the process advances, the toxic substances which damage the liver cells begin to act also on the incompletely differentiated cells (metahepatocytes). In the protoplasm of these immature cells aurophile bodies appear which are characteristic of cholechrysocytosis. Jaundice follows this morphologic change. The latter represents intrinsic depolarization of the cells.

In this paper the histologic alterations of the liver in cardiac disease are summarized as follows:

1. In cardiac patients dying with chronic passive congestion of the liver, no changes of any kind were found in the cells which could be related to the intensity of jaundice. Nevertheless, great numbers of metahepatocytes, easily recognized by their tonoplasmic reticulum, were found in those patients who had developed acute degenerative changes similar in type to those found in red atrophy of the liver.

2. To explain the absence of specific cellular changes usually related to jaundice and the abundance of metahepatocytes, we assume that the liver cells destroyed during chronic passive congestion are replaced by cells of the bile ducts. But in the patient with heart disease the liver cell is not subjected to any specific toxin and thus the metahepatocytes can continue their transformation into adult parenchymatous elements without acquiring cholechrysocytosis.

3. When jaundice appears in patients with heart disease, it is due to causes other than toxemia, the most important of which is the collapse of the intratrabecular bile capillaries in the more congested sites of the hepatic parenchyma.

4. The atrophy of the liver during congestive heart failure passes through the following stages: (a) congestion of the central venules with intense anoxia and moderate compression of the liver cells; (b) hyperplasia of the reticular endothelium forming the wall of sinusoidal blood capillaries; (c) elaboration of pre-collagenous fibers by this hyperplastic reticular endothelium; (d) intense compression of the trabeculae through spontaneous retraction of the recently formed fibers with collapse of the intratrabecular bile capillaries and compression atrophy of the liver cells; (e) fragmentation of trabeculae into isolated cells; (f) reabsorption of the isolated atrophic cells.

5. Jaundice appears only in those patients with heart disease in whom the following two fundamental conditions are fulfilled: (a) a sufficient number of intratrabecular bile capillaries have been collapsed; (b) the great number of cells which formerly evacuated their bile through the obstructed capillaries retain their functional integrity.

6. When the secreting pole of the compressed cells has ceased to exist, the bile and the other products of cell activity are shed into the bloodstream, causing the appearance of jaundice. The process of depolarization is extrinsic in nature since the chain of phenomena which reverses the flow is not in the secreting cell but arises from the mechanical obstruction of its normal draining mechanism.

7. The multiple miliary hemorrhages, commonly found in rheumatic disease as a consequence of the changes in the wall of small blood vessels, are sometimes the cause of extrahepatic jaundice, as shown by the Van den Bergh test. This form of jaundice is completely independent of the anatomic changes present in the liver of these patients.

CARDIAC CHANGES IN MALARIAL PATIENTS

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The authors made a careful cardiologic survey of a series of malarial patients, all of whom had positive smears for *Plasmodium*. The studies included clinical examinations, electrocardiograms, and radiographic examination.

Electrocardiographic and x-ray studies were made during apyrexia and before and after treatment. Abnormalities in the form and size of the heart and electrocardiographic changes noted before treatment tended to disappear in most of the cases when the disease was treated.

Anatomicopathologic studies were made in a patient who died of malaria. In the myocardium, dilatation and thrombosis of small capillaries were observed. There were no hemorrhages. Thrombi formed by masses of destroyed erythro-

cytes were present. In other places the capillary endothelium showed cytoplasmic changes with hyalinosis of the interstitial collagen tissue. Inside the thrombotic masses, as well as in the endothelial wall, numerous parasitic forms in various stages of evolution were found. Most forms belonged to the X erythrocytic and reticuloendothelial stages. Interstitial reactions around the capillary vessels were clearly observed near the epicardium and beyond the muscular tissue common to both ventricles. These reactions included hyalinosis of the pericapillary tissue, discrete hyperplasia of the collagen, and slight edematous infiltration. Interstitial reactions also included the formation of small nodules, consisting of histioid cells, better developed along vessels. These nodules had the characteristics of foci of reaction since young fibroblasts, small round cells, and plasma cells could be seen. Pericardial changes included some degree of edema, diffuse interstitial infiltration by histioid cells, and noticeable changes in the adjoining tissue. Lesions that are similar to the lesions described by the authors have been produced experimentally by Conejo and Libzchitz through infection with *Plasmodium gallinaceum*.

CIRCULATORY CHANGES RESULTING FROM OBSTETRIC LABOR

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The circulatory loads of pregnancy as determined by various workers have been summarized. The variable and undeterminable load of work of pelvic delivery is generally inconsequential but may be of such degree as to throw a considerable burden on the heart. After delivery, certain changes take place in pulse rate and blood pressure which suggest closure of an arteriovenous shunt. After delivery, effective blood volume transiently diminishes, then rises, and finally slowly returns to normal levels. The hematocrit changes indicate hemoconcentration in the immediate post-partum period. The venous pressure, while elevated for a prolonged period in patients with cardiac disease, is largely unaffected in normal individuals, except for rise following the use of pitressin or the ergot group of drugs. The dynamics of post-partum heart failure may be associated with unexplained changes in effective blood volume which could be due to transient pooling and then release of the pooled blood.

THE APEX CARADIOGRAM AND ITS UTILITY IN PHONOCARDIOGRAPHY

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In 1939, the author first pointed out the usefulness of the apex cardiogram in identifying the events of the phonocardiogram. For the purposes of this paper simultaneous records were made of the phonocardiogram and the apex cardiogram through a single cup.

The proper technique and the equipment required for making these studies is described. Typical graphic records are illustrated.

AN OBJECTIVE CLINICAL PROCEDURE FOR THE DETERMINATION OF CIRCULATION VELOCITY USING FLUORESCENT TRACER SUBSTANCES

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The clinical applications of circulation time measurements have been limited by the inability to determine minimal circulatory retardation. Localization of altered cardiovascular dynamics likewise has been difficult using the commonly employed techniques. These obstacles can be minimized by the newer tracer methods employing longer segments of the cardiovascular system. The purpose of this paper is to (1) demonstrate the use of riboflavin as a fluorescent tracer substance, (2) present a technique which renders circulation time of greater clinical value and, (3) demonstrate the value of comparative circulation velocities in various segments of the cardiovascular system.

Fluorescent media (riboflavin and fluorescein) were injected intravenously. The time was measured to the appearance of fluorescence in histamine wheals placed on various portions of the body. Fluorescence was excited by a 100-watt filtered ultraviolet light giving maximum emission at 3,600 Å°.

Arm-to-arm and arm-to-foot times were determined. The average difference between arm-to-arm times in normal subjects and in patients with congestive failure was only 18.9 seconds, whereas the average difference between arm-to-foot times in the same group was 42.3 seconds. These differences suggest that the arm-to-foot time is a more sensitive index of circulatory retardation than is the arm-to-arm time. The circulation time through a systemic arterial segment was computed by subtracting the arm-to-arm time from the arm-to-foot time: The normal average arterial circulation time was 9.5 seconds and varied between 7.5 and 11.2 seconds. Among borderline patients with subclinical congestive heart failure and in whom the arm-to-arm times were normal, the average arterial time was prolonged to 14 seconds. In clinically decompensated patients, the average arterial circulation time was 32.9 seconds and the range 14.9 to 59 seconds. The arterial circulation time did not exceed 12 seconds in normal individuals. A time greater than 12 seconds was suggestive of cardiac decompensation, even though the arm-to-arm time was within normal limits.

Mean velocities were computed for the three segments (arm-to-arm, arm-to-foot and arterial) by measuring or estimating the distance. It was found that the velocity in the arterial segment was the most sensitive index in comparing normal individuals and decompensated patients, the average difference being 7 cm. per second.

Prolonged circulation times (or decreased velocities) for the arm-to-arm and the arm-to-foot segments may be due to either right or left ventricular congestive failure or both; however, a prolonged arterial segment time may be due solely to left ventricular hypodynamic function. By the same token, a normal arterial segment time in the presence of prolonged arm-to-arm and arm-to-foot times may be due solely to right ventricular hypodynamic function. The measurement of circulatory velocities rather than circulation times is a desirable measure in estimation of altered cardiac dynamics because it eliminates the factor of distance over which blood travels in comparing the blood flow in tall and short individuals or in adults and infants. The principles involved in the localization of segmental dynamics may be applied to venous segments and to other portions of the arterial tree.

NOTE ON A PENTOSE ISOLATED FROM HEART MUSCLE

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It is generally believed that chemical changes in the heart muscle without accompanying histologic alteration may constitute the basis of functional disturbance.

Studies were made of the chemical constituents of the heart muscle of normal persons and of patients who died with heart failure. Drury's technique, modified by the authors, was followed. Cobra's venom was used as the hydrolytic agent. These investigations have revealed the presence in heart muscle of L-lyxose, a pentose not previously known to occur in organisms. The possible origin of this carbohydrate from alimentary mannose or galactose is pointed out.

DIFFERENT MECHANISMS OF FUSION BEATS

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1. A review is presented of the contributions to the understanding of the normal and abnormal spread of the cardiac impulse which have been revealed by the study of fusion beats ("transitional complexes," "combination complexes") in the electrocardiogram.

2. A classification of fusion beats is given, based on two criteria: origin of the fusing impulses and site of fusion.

3. The various mechanisms reflected in the electrocardiogram exhibiting fusion beats are discussed and illustrated.

4. A case of Wolff-Parkinson-White syndrome with auricular fibrillation showing complexes with a transitional contour (fusion beats) is presented as new evidence to demonstrate the functioning of both the normal and an accessory pathway in the Wolff-Parkinson-White syndrome.

SIGNIFICANCE OF VENTRICULAR OXYGEN CONSUMPTION AND
OF THE ENZYMATIC LIBERATION OF PHOSPHORUS IN
THE MECHANISM OF DIGITALIS EFFECT

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No significant changes in the use of oxygen by the normal left ventricle "in vitro" have been demonstrated to be caused by ouabain $1:10^6$.

There is a greater phosphorus enzymatic liberation in the myosin-adenosine triphosphate system of the heart if ouabain $1:10^6$ is present. The increase is even greater if calcium is added.

The importance of the enzymatic liberation of phosphorus as an explanation of the mechanism of action of digitalis glucosides in cardiac insufficiency is emphasized.

ON WRITING SYMBOLS TO DESCRIBE CARDIOVASCULAR SOUNDS
AND MURMURS WHILE LISTENING

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Auscultation of the heart can be practiced in at least two different manners. For one of these, this method of writing symbols to describe heart sounds and murmurs is of little or no value. For the other, it is indispensable. The observer who makes a diagnosis while listening by interpreting the total pattern of

sounds and murmurs and then writes his clinical notes in one or two brief phrases, such as "systolic murmur at apex, mitral insufficiency" or "mitral stenosis, presystolic murmur", will not be interested in using symbols for describing what he hears. On the other hand, the observer who carefully focuses his sense of hearing on each phase of the cardiac cycle, noting what he hears, needs a method to capture and hold each part of the cardiac cycle discovered as he analyses the heart sounds and murmurs. Thus, in searching the period just before the first sound for an auricular sound or murmur, and the first sound itself for duplication, then listening to the period between the first and the second sound for a mesosystolic sound or a systolic murmur, however faint, then noting the peculiarities of the second sound and, after it, searching for a third sound or a diastolic murmur, such an observer will find this method of writing symbols to describe what he hears indispensable in the practice of cardiac auscultation.

The symbols are designed to describe quantitatively the loudness and duration of each sound and murmur. For sounds, the symbols are rectangles; the vertical line (ordinate) represents loudness and the horizontal line (abscissa) represents the duration of the sound. For murmurs, waves of lines are drawn; the height represents loudness and the distance along the abscissa over which these are drawn represents the duration of the murmur. To represent high vibration frequency murmurs (blowing), the lines are drawn close together, and to represent low vibration frequency murmurs (rumbling murmurs), the lines are separated somewhat widely.

The observer writes while he is listening. This eliminates the element of memory as a source of error in describing objective signs. Bearing in mind an arbitrary standard symbol for loudness and duration of the first sound at the apex, he writes the symbols for what he hears in terms of this standard.

A full description of everything heard in a case with buttonhole mitral stenosis and aortic stenosis and insufficiency would require about 320 words, ten minutes to write them, and three minutes to read them. The record written in terms of symbols is made while the observer listens and can be read at a glance.

STUDIES ON THE HEART SOUND IN MITRAL STENOSIS

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During the last six years more than two hundred patients with mitral stenosis were studied in the Hospital Central Militar. The studies included clinical examination, x-ray examination, laboratory studies, electrocardiograms, and phonocardiograms. In some cases necropsy examinations were made. In seven patients with mitral stenosis, phonocardiograms were recorded at many different sites across the precordium. These sites were then marked with a lead disc and recorded upon an x-ray film.

No clear difference was found between "rumbling sounds" and "murmurs." The former were lower pitched (80 to 100 vibrations per second) and occurred in the first part of diastole; the latter were higher pitched (100 to 150 and even 200 vibrations per second) and appeared toward the end of diastole (presystole). In some patients a low-pitched presystolic murmur was heard and recorded and in others an early high-pitched diastolic murmur was present. In some patients the systolic and the diastolic murmurs were found to be of the same pitch and of almost the same duration. In other patients the systolic and the diastolic murmurs merged into a "machinery" murmur. In still others the systolic and the presystolic murmurs were continuous and gave the impression of a single murmur. In many patients with mitral stenosis, proved by x-ray examination

and even by necropsy, no murmur was heard. In some patients with both mitral stenosis and insufficiency only the systolic murmur was clearly audible and recorded.

The "opening snap" was frequently recorded. The "snapping" quality of the first heart sound was often detected; in some patients it constituted the only stethoacoustic evidence of mitral stenosis. The reduplication of the second heart sound and an audible third heart sound were often heard and recorded but neither sign was characteristic.

The diastolic murmur was heard best mainly in the fourth intercostal space 4 cm. to the left of the sternal margin, but was heard often in the fifth intercostal space. Presystolic murmurs were heard best at the apex or slightly above and internal to the apex. The opening snap of the mitral valve was recorded better in the fourth intercostal space over the left border of the cardiac silhouette.

THE FIRST CARDIAC SOUND IN PREMATURE CONTRACTIONS

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Auscultation and phonocardiographic studies in thirty instances revealed that the first cardiac sound in premature contractions is generally more intense than in preceding and subsequent normal contractions.

This increase of intensity of the sound occurs most often with auricular extrasystoles; it is less frequent with ventricular extrasystoles. In the latter, however, splitting of the sound is sometimes found and may be diagnostic.

It is suggested that the phenomenon is the result of the relaxed and dependent position of the auriculoventricular valves during the moment of production of the premature systole.

SYMPATHOMIMETIC AMINES IN THE HEART MUSCLE: THEIR PATHOGENIC AND THERAPEUTIC SIGNIFICANCE

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Several thousand determinations of epinephrine-like compounds were carried out in blood and tissues with a modification of Shaw's colorimetric method. The results agreed well with quantitative biologic tests for sympathomimetic amines originating both in the adrenal medulla and in the entire sympathetic system (epinephrine, sympathin, and related compounds).

Increases of this material in the heart muscle of animals were found under the following conditions: electrical stimulation of the stellate ganglia and of the splanchnic nerves; injection of epinephrine and acetylcholine; physical exercise; exposure to cold temperature; thiamine deficiency. On the other hand, decreases of these compounds in the myocardium were elicited by sympathetic denervation of the heart, total sympathectomy, adrenalectomy, or combinations of these.

It was found that excessive accumulation of sympathomimetic material in the myocardium above a sharply defined critical limit is inevitably fatal in the rat through acute heart failure. Results obtained in the hearts of patients with and without cardiac disease indicate that in man the tolerance limit is somewhat lower.

Abnormally intense discharges of epinephrine-like substances into the blood during exercise were regularly observed in patients with angina pectoris on effort and, frequently, in patients with essential hypertension. In advanced

uremia the blood level of such substances is always considerably elevated and the uremic serum proved to be highly cardiotoxic.

The myocardial concentration of epinephrine-like material increases with age, reaching a maximum in the sixth decade. Abnormally high concentrations were found in hearts of patients who had died from heart failure, in one case of adrenal medullary tumor, in two cases of sudden death in young persons without morphologic pathology, and in uremic hearts.

These observations suggest a fundamental significance of the excessive accumulation of adrenosympathetic amines in the heart muscle for the pathogenesis of "degenerative" heart disease, angina pectoris, sudden cardiac death without coronary sclerosis, uremic cardiac death, and the beriberi heart.

This conception is supported by the well-known analogies between the electrocardiographic, myocardial metabolic, and structural changes produced by repeated experimental epinephrine injections and the corresponding features in "degenerative" heart disease, angina pectoris, uremia, and the beriberi heart. Furthermore, the typical occasion for angina pectoris attacks (exercise, emotion, exposure to cold) are the same which are known to elicit adrenosympathetic discharges.

The sensitization of the heart to sympathomimetic amines through the thyroid hormone, which is probably involved in the features of the thyrotoxic heart, was demonstrated by a marked lowering of the fatal myocardial threshold for epinephrine in thyroxin-treated animals.

Rational therapeutic procedures deductable from these conclusions are as follows:

1. Desensitization of the heart through elimination of the sensitizing thyroid hormone through thyroidectomy or thiouracil. The latter drug was shown to protect the heart against otherwise fatal doses of epinephrine, to diminish or abolish the effects of epinephrine injection on the normal electrocardiogram, and to free patients with angina of their symptoms for weeks or months after sufficiently long periods of treatment.

2. Pharmacologic counteraction against the effects of sympathomimetic amines. Benzyl-imidazoline and, particularly, dibenzyl- β -chloroethylamine hydrochloride, proved highly potent in protecting the hearts of animals against fatal doses of epinephrine. Their clinical usefulness remains to be studied.

3. Suppression of excessive adrenosympathetic discharges. (a) Roentgen irradiation of the adrenal glands abolished the exercise-induced abnormal sympathomimetic discharges in patients with angina and was followed by partial or complete relief for years in the majority of 150 cases. It tended to normalize the electrocardiograms of these patients partially or completely. (b) Lumbo-dorsal sympathectomy in patients with hypertension is often followed by a normalization of the pathologic electrocardiogram, even if the hypertension remains unchanged, probably due to a diminution of the influx of sympathomimetic amines into the heart, as is also seen in animal experiments.

It is becoming increasingly evident that some of the most common forms of heart disease which, by tradition, used to be attributed solely to hemodynamic factors, such as blood pressure, impaired coronary flow and the like, are primarily caused by biochemical processes in which the sympathomimetic amines play a dominant role.

THE CARDIAC ACTION OF CENTRAL AMERICAN SNAKE VENOM

E. GARCIA CARRILLO, M.D., ACTIVE MEMBER, COSTA RICA

The effect of snake venom on the electrocardiogram has not heretofore been thoroughly studied. The author presents his findings in eleven patients who were bitten by Central American Snakes of the genus *Bothrops* which are the common species in Tropical America. In a study of eight thousand autopsies, only ten deaths were attributed to the venom of *Bothrops atrox* and *Bothrops schlegelii*.

The electrocardiographic pattern in the stricken individuals was characteristic and consisted of (1) T wave of small amplitude with a rounded vertex in one or more leads, (2) slight depression of S-T in CR₅, (3) a prolonged Q-T interval. When toxic symptoms are lacking, electrocardiographic changes are absent or slight but always show the same tendency. The author suggests that the effects of snake venom on the heart could be attributed to vascular lesions, nervous influences, coronary insufficiency secondary to anemia, or to biochemical changes. He also makes the interesting suggestion that the electrocardiographic changes may be caused by changes of cellular permeability to potassium.

AN IMPROVED ELECTRIC MANOMETER FOR MEASURING THE INTRA-ARTERIAL, INTRAVENOUS, AND INTRACARDIAL PRESSURE, WITH A GENERAL THEORY OF MANOMETERS

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Buchta and Warburg's condenser manometer has been redesigned by Tybjaerg Hansen with the result that the manometer in its present design yields the maximum efficiency attainable for manometers intended for blood pressure measurements by means of arterial punctures and catheterization of the heart.

The manometer is shown in Fig. 1 of the complete paper.

Due to the small, very rigid phosphor-bronze plate (thickness, 0.3 mm.; surface area, 1 cm.²) forming the yielding component of the manometer, the system is very rigid, displacements being only 0.1 c.mm. at 100 mm. Hg pressure. The movements of the plate are transmitted electrically. The plate, together with a block of brass from which it is separated by a space of the width of 15 micra, forms a condenser, the capacity variations of which are caused to work in an oscillograph by means of a high frequency arrangement and a direct current amplifier.

The modulus of elasticity (E') of the manometer is 3.3×10^9 dynes.

The compressibility of the water at this rigidity produces 40 per cent of the total change in volume (the capacity of the manometer is 2.0 c.c.).

A general theory of manometers has been evolved, the damping term having been introduced into Frank's equation of manometers.

The manometer equation of free oscillations is thus:

$$\frac{L}{\pi r^2} \cdot \frac{d^2 y}{dt^2} + \frac{8 \eta L}{\pi r^4} \cdot \frac{dy}{dt} + E' \cdot v = 0$$

Only the modulus of elasticity, the syringe needle used (probe, catheter), and the viscosity of the liquid are decisive to the dynamic constants of the manometer.

- L = Length of the needle
- r = Radius of the tube
- η = Viscosity of liquid in poise
- v = Volume change
- E' = Modulus of elasticity of the manometer

Formulas are given for determining the natural undamped and damped frequency, as well as the degree of damping of the manometer and needle, and it is shown that a needle having a length of 5.5 cm. and a bore of 0.22 mm. gives an undamped natural frequency of approximately 60 and a damping degree of approximately 0.7, which are the appropriate magnitudes for recording pulse curves. The relation between degree of damping and amplitude is demonstrated. In the case of a probe having a length of 60 cm. and a bore of 1 mm., the undamped natural frequency is approximately 100 and the damping degree is 0.22. An extra damping should be introduced into such a system. A capillary tube of a length of 2.5 mm. with a bore of 0.1 mm. will give an undamped natural frequency of 86, the damping degree being 0.7, which is the optimum.

An easy method has been described for determining the undamped natural frequency and damping degree of the system by means of sudden and constant variations in pressure. On the basis of the formula of the transitorial part of an oscillating system, it has been shown to be convenient that the manometer has an overshoot between 5 and 10 per cent.

Pulse curves recorded by means of the manometer are demonstrated.

MEDICAL-SOCIAL FEATURES OF HEART DISEASE IN CHILE

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The author studied the frequency, etiology, and commonest types of heart disease in Chile. The data upon which these studies were based were gathered from medical examinations made on workers, as required by the Preventive Medicine Law which is enforced in the whole country.

Heart diseases seem to be more prevalent in office workers (10.65 per cent) than in those who engage in common labor (4.38 per cent). High blood pressure, arteriosclerosis, rheumatic heart disease, and syphilitic heart disease are dominant causes of cardiovascular diseases in the entire population.

A classification of cardiovascular affections, which is based upon functional ability and is, therefore, essentially a medical-social classification, is proposed. Most patients belong to Types I and II of the classification and receive periodical clinical examination. Patients belonging to Type III are submitted periodically to preventive rest and treatment. Patients belonging to Type IV are made to retire from activities that are beyond their limited physical abilities.

The author analyzes the conditions under which preventive rest is applied and the immediate results of this benefit. Generally speaking, it can be stated that after an average period of three months' rest, 70 per cent of the patients with heart disease can resume work.

ATTACKS OF UNCONSCIOUSNESS RESULTING FROM HYPERACTIVE CAROTID SINUS REFLEX

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A study was made of eighty-five patients with hyperactive carotid sinus reflex. Most of the patients were treated medically. Operation was performed on twenty-one patients. A brief discussion is given of the anatomy, nerve supply, and function of the carotid sinus. In the series of patients studied at the Mayo Clinic, the ratio of males to females was 5:1. The average age of the patients was 56 years. The chief symptoms were vertigo and unconsciousness; mild convulsion may be associated with the syncopal attacks. Attacks occasionally are precipitated by changing the position of the body, turning the head to the right or left, or looking upward. Any pressure on the neck, such as tight collars or carrying sacks of grain on the shoulders, also may bring on attacks. In most instances, however, the precipitating factors in the spontaneous attacks are unexplained.

The incidence and the severity of the attacks varied greatly. They varied from an occasional mild attack occurring once or twice a year to severe spells occurring many times a day.

If the symptoms are mild, no treatment is required other than reassurance. If the attacks interfere with the patient's work, he should be instructed to avoid turning his head quickly, looking upward, or stooping suddenly. He should avoid any constriction about the neck. Drugs have not been particularly satisfactory; phenobarbital has given the best results. If the attacks are severe and a thorough course of medical management has not been successful, complete denervation of the carotid sinus may be performed, but this procedure has not been entirely satisfactory.

EXPERIMENTAL AND CLINICAL STUDIES IN HYPERCHOLESTEROLEMIA AND ATHEROSCLEROSIS AND THE EFFECT OF DECHOLESTEROLIZING AGENTS

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It has been demonstrated that pancreatic substances and lecithins, choline, inositol, and methionine prevent and correct nutritional fatty disorders in the liver and kidney, presumably by mobilization or changing of cholesterol to more easily metabolized lecithins and lipid phosphorus. It seemed that the same decholesterolizing substances might probably effect the cholesterol in the blood plasma and possibly the cholesterol in subintimal atheromatous plaques.

In order to test this hypothesis, several control and experimental series of twenty-four 3-year-old hens of high egg-producing stock were maintained on the standard laying mash and studied. Hypercholesterolemia and high tissue cholesterol levels had been demonstrated in various control series of these old hens. In two series the additional feeding of choline chloride in 0.5 Gm. doses to twenty-six old hens of the same breed showed fairly regular reduction of cholesterol levels in the blood and in the aorta, heart muscle, and liver. The administration of inositol, 0.5 Gm. doses, to another series of 3-year-old hens had less, but still some, decholesterolizing effect. The administration of methionine in 0.5 Gm. doses per day to two other series, a total of twenty-three 2-year-old hens, had seemingly the greatest decholesterolizing effect.

In patients with hypercholesterolemia and coronary artery disease, the restriction of animal fats in the diet and the administration of potassium iodide and of thyroid extract have been shown to lower blood cholesterol levels after

six months to two years. The administration of choline, methionine, and inositol has produced, in a majority of patients, some reduction of blood cholesterol levels and slight rises in lipid phosphorus after two to six months of treatment. The basic diet is of considerable importance and in some refractory cases, the exhibition of other substances is probably necessary to accomplish decholesterolization. The enzyme system or systems responsible for the mobilization and degradation of cholesterol to lecithins are still unknown.

The present concepts of the factors concerned in the development of atheromatosis are incomplete. There has opened up at least one and possibly more new approaches to the prevention, postponement, arrest, or possibly decrease of the subintimal plaques. These plaques in secondary arteries are very often of such serious significance. Dietary restrictions of the sterol intake and the use of potassium iodide and thyroid extract judiciously in selected cases seem justified. The success of administration of the newer decholesterolizing agents seems to offer another promising method of therapeutic attack on the serious processes of premature aging.

STUDY OF CEREBRAL AND PERIPHERAL EMBOLI, REGISTERED IN THE NATIONAL INSTITUTE OF CARDIOLOGY OF MEXICO, FROM SEPTEMBER, 1944, TO MAY, 1946

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A study was made on twenty-five patients with embolism. These included seventeen emboli to the brain, ten to the peripheral arteries, and one to the retina. The percentage among individuals with rheumatic heart disease was 1.35; among individuals with auricular fibrillation, 9.43; among individuals with bacterial endocarditis, 5; and among those with myocardial infarction, 2.08 per cent.

The difference between peripheral embolism and thrombophlebitis cannot be easily established because both are often found in cases of rheumatic fever, auricular fibrillation, and heart failure, and both bear a very close clinical resemblance.

The differential diagnosis in cerebral involvement has been established as follows: Brain hemorrhage is seen in young patients with active rheumatic fever in whom the neurological picture is serious and not well defined. Embolism occurs in older individuals with advanced heart disease in whom hemiplegia or aphasia or both are found. In these older individuals with emboli, infection is not important.

The gravity of the vascular accident depends upon the size of the embolus, upon whether it is placed in an important artery, and upon whether there are multiple emboli in large arteries. When the latter is the case, the outcome is less favorable.

CLINICAL IMPRESSION OF THE THERAPY IN THROMBO- ANGIITIS OBLITERANS

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This is a report on 278 patients with thromboangiitis obliterans seen during the past thirteen years in the New York Post-Graduate Hospital Vascular Clinic and in the offices of some of the group associated with the Clinic. The purpose of presenting this paper is to give our clinical impressions of the effects of therapy in these patients. The patients were carefully checked in order to rule out those who did not have true thromboangiitis obliterans. In each in-

stance, the age, sex, nationality, background, habits, and emotional status of the patient were noted.

Because the etiology of the disease is unknown, we turn to the pathology and pathologic physiology for an appreciation of what can be accomplished and expected from therapy. Thromboangiitis obliterans is a true angiitis with an associated venous thrombosis and an inflammatory lesion of the accompanying nerve. With this last factor added, we have a chain of events that makes for multiple problems; arterial, venous, arteriolar, and sympathetic, not to mention the psychosomatic. The elimination of pain, inflammation, ischemia, and gangrene are the main concern.

Our routine therapy consists of no smoking, an oscillating bed, potassium permanganate (1:5000) soaks at 90-94° F. daily for twenty minutes, typhoid vaccine intravenously, sterile dressings, protection of the limbs, heels, etc., and sedation and whiskey.

In setting up the rules for therapy, the complete elimination of tobacco has been a rigid rule. Not all patients live up to this. It has been our experience that if they do, in most patients, pain will cease and lesions will begin to heal almost from the start. On the other hand, let the patient recommence smoking and the pain will recur and lesions will become active and will not heal.

Pain, a very real problem in thromboangiitis obliterans, is markedly decreased by intravenous typhoid vaccine. In our experience, this has occurred too often to be coincidental.

The meticulous care of the feet is probably one of the most important forms of therapy. Care of the corns, nails, and calluses must be emphasized. A neglected callus or ingrown toenail may be the antecedent to an amputation.

The extremity with an open lesion needs rest. This should be physiologic in nature; that is, six inches below heart level, or "Buerger type," or that afforded by an oscillating bed; the extremity should never be elevated. We feel at present that the ideal temperature for those extremities is 80 to 84° F. Our opinions regarding refrigeration are in a state of flux. We have not been successful in saving limbs from amputation by refrigeration, once it became obvious that gangrene was inevitable. The scrupulous care of the small or early lesion is important. Protection of the extremities at all times is necessary. The patient must be taught to live within the capacity of his limited blood supply, and to carry out the therapy outlined faithfully.

We have come to the following conclusions:

1. Patients who stop smoking can be assured a remission in their disease, which can and does last for years with no need for any form of therapy other than abstinence from nicotine. No therapy, regardless of what is given or the amount, is of sufficient magnitude to overcome the bad effect of tobacco.
2. Hygiene of the feet is important. It may be that fungous infections sensitize the tissues, or that the cracks in the skin are the opening wedge for streptococcus and staphylococcus infection with their sequelae.
3. If we can educate the patients with thromboangiitis obliterans to stop smoking and live within the capacity of their impaired blood supply, no further therapy is needed.

INCIDENCE AND CLINICAL FEATURES OF RHEUMATIC FEVER IN MEXICO CITY

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The author studied the clinical characteristics of rheumatic fever in 750 patients in order to establish the special features of the disease as seen in Mexico. The incidence of the disease was computed from a careful analysis of 2,000 post-

mortem examinations, as well as from a study of the clinical records of patients observed at the Instituto Nacional de Cardiología de Mexico.

Of the 750 patients with rheumatic disease, 66.2 per cent were women. The main symptoms were noted as follows: carditis, 93 per cent; arthritis, 61.8 per cent; chorea, 13 per cent; subcutaneous nodules, 7.8 per cent; and rheumatic erythema, 2.4 per cent. The following secondary manifestations were recorded: anemia, 57.7 per cent; joint pain, 52.7 per cent; loss of weight, 50.3 per cent; asthenia, 47 per cent; epistaxis, 26.8 per cent; adynamia, 19.2 per cent; muscular pain, 18.6 per cent; torticollis, 16.8 per cent; chest pain, 9 per cent; fever not associated with arthritis, 8.9 per cent; purpura, 2.2 per cent; and abdominal pain in 1.2 per cent. The commonest combinations of symptoms in rheumatic fever were: arthritis and carditis, 48.4 per cent; carditis alone, 32.4 per cent; carditis, arthritis, and chorea, 7.4 per cent; carditis and chorea, 5.2 per cent; arthritis and chorea, 0.2 per cent.

It could be observed that chorea appeared, on the average, in the first decade of life, while arthritis tended to appear ten years later, and carditis a little less than twenty years afterward. On the other hand, nervous (chorea) and joint symptoms remained only for months, while carditis showed activity for years.

Arthritis was recorded as the initial symptom of rheumatic fever in 50 per cent of the patients, carditis in 37.4 per cent, and chorea in 8.8 per cent. There was an average interval of eight years between the first and the second attack of rheumatic fever.

Valvular involvement occurred in the following proportions: a double mitral lesion was recorded in 52.5 per cent; mitral stenosis in 21.3 per cent; mitral disease and aortic insufficiency in 6.6 per cent; mitral and aortic involvement in 4.7 per cent; mitral insufficiency in 3.8 per cent; mitral stenosis and aortic insufficiency in 2.1 per cent; mitral and aortic insufficiency, 1.9 per cent; mitral insufficiency and aortic disease in 1.7 per cent; and aortic insufficiency alone in 1.2 per cent. The tricuspid and pulmonary valves were involved in a very small percentage of the cases.

Patients with polyarthritis gave the following symptomatology: pain in 97.8 per cent; delirium in 96 per cent; phlogosis in 86.2 per cent; fever in 82 per cent; migration of the joint involvement in 70.9 per cent; and diaphoresis in 69.1 per cent. The involved joints were as follows: knees, 63 per cent; ankles, 58 per cent; elbows, 34.9 per cent; wrists, 31.4 per cent; fingers, 21.5 per cent; shoulder, 21.4 per cent; all joints, 20 per cent; hips, 6.3 per cent; spine, 5.7 per cent; sacroiliac, 3.3 per cent; and temporomandibular, 1.3 per cent.

Rheumatic fever appeared most often during the winter and spring months. The onset of rheumatic attacks was associated with infections due to hemolytic streptococcus in 61.7 per cent. In 87 per cent the antistreptolysin titer was found to be high, and in 38 per cent of the cases, the hemolytic streptococcus was recovered from the nasopharynx of the patients.

In 31.4 per cent of the relatives of patients with rheumatic fever there was a history of some rheumatic symptoms; in 9.8 per cent there was a definite history of rheumatic fever. No other particular disease could be found in the relatives of the rheumatic patients which could be incriminated as a predisposing factor to the rheumatic infection. Poverty, however, existed in 47.6 per cent of the patients.

Rheumatic fever is not rare in the temperate and even tropical zones of Mexico. The post-mortem incidence was 11 per cent; the figure rose to 38 per cent in the patients studied at the Instituto de Cardiología de Mexico.

The clinical features of rheumatic fever in Mexico are much like those described in other countries. Its high incidence justifies a definite program for its control.

IS THE ORTHODOX THERAPY OF RHEUMATIC FEVER CONDUCTIVE TO PSYCHOSOMATIC DISABILITY?

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1. The nature of rheumatic fever has been briefly considered and the probability of psychosomatic or functional disability resulting inadvertently from, or at least during, the course of orthodox management of this disease has been pointed out.

2. The preventable nature of these disabling conditions is apparent.

3. Adequate therapy can probably be accomplished with a lesser period of bed rest than was formerly thought necessary.

4. Through adequate psychologic understanding and the practice of intelligent psychotherapy, we as physicians can prevent at least part of the disability resulting from rheumatic fever.

CLINICAL FEATURES OF 1,160 CASES OF RHEUMATIC VALVULAR ENDOCARDITIS

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The authors studied 5,665 clinical and 250 post-mortem records of patients seen up to 1946 at the Cardiological Institute. This material included 1,809 subjects without heart disease. A diagnosis of rheumatic endocarditis was made in 1,225 patients, although only 1,160 clinical records were of interest for the present study. Of all cases examined post mortem 147 displayed rheumatic endocarditis.

Analysis of these records allows the following conclusions:

1. Rheumatic endocarditis occurred in 30.9 per cent of the cardiac patients.

2. Of these, 63 per cent were women.

3. No racial characteristics which predispose to rheumatic heart disease were noted.

4. A history of rheumatic fever in consanguineous relatives was definite in 10.9 per cent of the cases and doubtful in 2.6 per cent.

5. A history of rheumatic fever was recorded in 56 per cent of the cases; a history of chorea was present in 13.1 per cent.

6. Rheumatic heart disease without a history of rheumatic fever occurred in 65.5 per cent of patients.

7. The first attack of rheumatic fever appeared between the ages of 11 and 20 years in 46.8 per cent of the cases; of those who had chorea the disease occurred between the ages of 6 and 10 years in 57.2 per cent of the cases.

8. Joint pain was the prevalent symptom of rheumatic fever (51.4 per cent); other symptoms in order of frequency were tonsillitis, 50.6 per cent; epistaxis, 28.7 per cent; torticollis, 20.3 per cent; muscular pain, 20.1 per cent; conjunctival hyperemia, 7.4 per cent; and abdominal pain, 2.8 per cent.

9. The clinical diagnosis of valvular involvement was as follows: mitral in 1,122 cases, 96 per cent; aortic in 209 cases, 18.0 per cent; tricuspid in 20 cases, 1.7 per cent; and pulmonary in none.

10. Of the 1,160 patients, 44.1 per cent had symptoms of cardiac failure.

11. Heart failure was most often seen between the second and the fourth decade of life; failure was particularly prone to develop from three to ten years, and from sixteen to twenty years after the first rheumatic attack.

12. Disturbances of rhythm were found in 203 patients, 193 with auricular fibrillation and ten with auricular flutter. Conduction disturbances were re-

corded in sixty-nine patients: forty-nine with first degree, three with second degree, three with complete A-V block, and fourteen with bundle branch block. In 97.9 per cent auricular fibrillation coexisted with mitral stenosis.

13. Rheumatic heart disease coexisted with other forms of heart disease as follows: with congenital defect, 0.5 to 0.8 per cent; with syphilitic heart disease, 8.7 to 9.9 per cent; with bacterial endocarditis, 1.5 to 2.4 per cent; and with hypertensive heart disease, 3.6 to 6.0 per cent.

14. Valvular calcification was diagnosed clinically in 0.7 per cent of the rheumatic series. The post-mortem examinations revealed calcification in 1.4 per cent.

15. Complications were diagnosed as follows: pericarditis, 1.3 to 2.0 per cent; pleuritis, 0.9 per cent; pulmonary infarct, 1.2 to 1.4 per cent; peripheral embolism, 3.5 to 4.5 per cent; and renal involvement, 2.3 per cent.

16. The average age at which death occurred was 24.5 years. The greatest mortality occurred between 11 and 40 years of age, and particularly between 11 and 20 years of age (38 per cent).

17. The most frequent cause of death was cardiac failure (72.7 per cent).

18. Lack of correlation between clinical diagnosis and post-mortem findings was essentially due to the large incidence of tricuspid lesions (33.3 per cent); only 8.1 per cent of these were diagnosed clinically.

19. The complications found at post-mortem examination were pericarditis, 29.9 per cent; renal infarct, 27.8 per cent; pleuritis, 19.7 per cent; splenic infarct, 17 per cent; intracardiac thrombosis, 12.2 per cent; cerebral hemorrhage, 10.8 per cent; bacterial endocarditis, 8.8 per cent; and cerebral embolism, 8.1 per cent. Most of these complications coexisted with mitral valvular involvement, particularly mitral stenosis.

20. Mistakes in diagnosis as proved by the post-mortem examinations were twelve (8.1 per cent). Most often a mitral lesion was confused with aortitis or cardioangiosclerosis.

21. Among 127 patients over 44 years of age, the most common lesions found were mitral stenosis and mitral disease.

22. Since syphilis coexisted frequently in this older group of patients (23.6 per cent proved and 28.3 per cent doubtful) and since most erroneous diagnoses occurred in this same group, it is emphasized that in older patients the history as well as all clinical manifestations must be carefully considered before a final diagnosis of the nature of the valvular disease is made.

ENCEPHALOPATHY OF THE RHEUMATIC PATIENT

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The authors describe thirty-two patients in the children's ward at the National Institute of Cardiology who had encephalitic symptoms during the course of rheumatic fever. Two types of symptoms were noted: in the first type sudden coma developed and was followed by death; in the second, psychomotor instability, obtundation, and disturbances of sleep were observed. This state may continue for several days, often ending in sudden death.

Of one hundred fifty-one cases of rheumatic fever which were studied post mortem, 107 of the patients had pathologic changes involving the brain. Thirty-two of these were children. The encephalitic changes consisted of edema, swelling and wet appearance of the brain tissue, hyperemia, punctiform hemorrhages, and free liquid. In a large percentage there was no parallelism between peripheral and brain changes.

The changes found are not considered as specific for rheumatic fever, for they occur in many other infectious and toxic states and in conditions associated with anoxia. Cranial hypertension is thought to be the immediate cause of death. The authors propose the name rheumatic encephalopathy to describe the symptomatology. By way of treatment massive doses of oxygen are recommended, as well as all other known general measures.

THE SIGNIFICANCE OF INTERSTITIAL LYMPHOCYTOSIS IN RHEUMATIC DISEASE AND IN OTHER INFLAMMATORY PROCESSES

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Rheumatic disease behaves in a very different manner in young people and in adults. It can, therefore, be considered that the disease has, in common with other diseases with an intense allergic component such as tuberculosis, two well-defined periods. The first or initial period, which tends to be prevalent in children and adolescents, has as its characteristic features severe changes in the small vessels, a subacute course, and production of death as a consequence of encephalitic changes (rheumatic encephalopathy, described by Gortari, Pellon, and Costero). The second period is seen when the disease is well established and occurs in adults. This stage is distinguished by the presence of lesions affecting mainly the endocardium, the large vessels, and the serous membranes of the joints. It runs a chronic progressive course and tends to recur. The second stage often follows the initial period and frequently leads to heart failure.

Corresponding to these two symptomatic types, rheumatic disease presents two different types of anatomic lesions: (1) Aschoff nodules and equivalent inflammatory granulomas which are abundant during the initial period and which represent a hyperergic reaction, and (2) lymphocytic infiltrations within the affected organs which are seen during the second period of the disease and are of unknown significance. It is the aim of the present work to suggest an anatomic and physiologic basis for the existence of such lymphocytic infiltrations.

1. Lymphocytic infiltrations are generally considered to represent a chronic inflammation. It is important, however, in order to facilitate the interpretation of this phenomenon, to distinguish genuine inflammation from spurious inflammation. Genuine inflammations are those which are accompanied by clinical symptoms suggesting infection, by lymphangitis, lymphadenitis, septicemia, toxemia, sapremia, and by other manifestations such as fever, antibody formation, changes affecting the white blood cells, and an increase in the blood sedimentation rate.

In spurious inflammations there are usually no manifestations of infection nor general alterations such as fever, antibody formation, and white blood cell changes. If these alterations are present in spurious inflammations, they are of subclinical intensity and are discovered only after careful investigation. The spurious type of inflammation may be divided into two different groups: (1) The so-called physiologic inflammation (Rössle) which is present during digestion and menstruation, and (2) the changes that accompany repair of inflammation following parenchymatous atrophy and those that develop where compensatory hyperplastic reactions occur, as, for example, in hydronephrosis following sudden obstruction of the ureter.

Genuine inflammation is not accompanied by lymphocytic infiltrates prior to the initiation of regenerative phenomena. In so-called physiologic inflammation the lymphocytic infiltrate constitutes the main feature of the anatomic lesion, and in the healing stage of inflammation it is frequently the only change found.

2. The phenomena of inflammation can be divided into three different types: alterative, exudative-infiltrative, and proliferative (Lubarsch). These phenomena are probably produced by the action of diffusible substances formed by disintegration of tissue and receive the names of phlogotoxins, phlōgoangins, and phlogotrophins (Costero). Phlogotoxin corresponds to Menkin's necrosin; similarly, phlōgoangins correspond to Menkin's leucotaxine and leucocytosis-promoting factor, as well as to the H substance of Lewis and Grant; phlogotrophins have not yet been isolated.

3. The endothelium of blood and lymphatic capillaries is impermeable to proteins of large molecular weight. Lymph contains a large amount of protein of large molecular weight. Our present knowledge suggests that proteins in the lymph are derived from cellular substance.

4. (1) Cellular extracts as well as some complex proteins behave experimentally as lymphocytogenic substances and provoke reticular hyperplasia (Wiseman). (2) Reticular cells control the metabolism of proteins of large molecular weight. (3) Under normal conditions, lymphocytes arise from reticular cells of the lymphadenoid tissue. One may suggest, in the light of these facts, that nodal lymphopoiesis is a response to proteins carried from the tissues to the nodes by the lymph.

5. In inflammation, the lymphocytic infiltrate is derived from local histiocytes (Mollendorff, Siegmund, Klinge, Maximow, Downey and Weidenreich, etc.), which may be considered homologous to the reticulum cells of the lymph nodes. Local lymphopoiesis must be stimulated by proteins derived from cells undergoing regressive or regenerative changes which alter protoplasm. This statement is borne out by (1) the relationship between the intensity of cellular repair and the degree of lymphopoiesis; (2) the increase of local lymphopoiesis when normal flow of lymph is made difficult, as in lymphadenitis; (3) the interdependence between local lymphopoiesis and the presence of pathogenic organisms; (4) the impossibility of avoiding the development of elephantiasis in lymphatic edema. When purely lymphocytic infiltrations are found within the tissues, one cannot speak of genuine inflammation, since local or generalized manifestations of inflammation are absent. This occurs during hydronephrosis following obstruction of the ureter, in diffuse glomerulonephritis, in atrophic cirrhosis of the liver, etc., when the anatomic lesions of the tissue are duly compensated. The static period of rheumatic disease belongs to this variety of spurious inflammation.

6. In rheumatic disease, as in other inflammatory processes, the lymphocytic infiltrates represent an index measuring the intensity of local cellular destruction. This is not related to the degree or the presence of pathogenic organisms or to any other cause of inflammation.

7. Since in the second stage of rheumatic disease local lymphocytic infiltrations are constantly present, one has to suspect the existence of permanent metabolic changes within the affected tissues. These metabolic changes are manifested not only by local lymphopoiesis, but also by proliferative phenomena with histiocytic proliferation. The differentiation of histiocytes results in a blockade by changes in the histiocytic system. This blockade leads to a remarkable diminution of the defensive capacity of the histiocytic system and local infections are thus facilitated. This is the rule in patients with rheumatic disease. On the other hand, complications of the same type have been observed in elephantiasis and in many other pathologic processes accompanied by local lymphocytosis and differentiation of histiocytes.

8. Infectious diseases never leave persistent metabolic alterations in the tissues. Such alterations are seen only in allergic diseases and in some infections

produced by filtrable viruses. In such cases and in rheumatic disease, the anatomic lesions may be interpreted as a form of premature autochthonous aging of the system or systems affected by the disease.

ON THE INTRAVENOUS USE OF MORPHINE IN THE TREATMENT OF PAROXYSMAL VENTRICULAR TACHYCARDIA

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A case of ventricular paroxysmal tachycardia, which was not affected by intravenous quinidine, promptly responded to morphine administered intravenously. Since this observation, the author has used the drug routinely in all cases of ventricular paroxysmal tachycardia. The author points out that patients with paroxysmal ventricular tachycardia suffer some degree of peripheral collapse which makes the absorption of morphine, given subcutaneously, uncertain. Of ten cases reported, nine of the patients responded to morphine treatment. The dose varied between 1 and 4 centigrams of morphine; the interval between doses was one-half to two hours. Favorable effects were observed from ten to thirty minutes after the injection. No undesirable effects were produced. A very hypnotic action of drug was observed.

The only instance in which morphine failed to give relief was in a patient in coma with severe peripheral collapse, who had been treated unsuccessfully with quinidine. The patient died thirty-six hours after coming under the author's observation.

DIGITALIS AND QUINIDINE IN THE TREATMENT OF AURICULAR FIBRILLATION

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The value of quinidine in the treatment of acute and chronic auricular fibrillation is fairly well established. Perhaps not enough emphasis has been put upon the part digitalis plays (1) in the preparation of the heart before starting with quinidine; (2) during the active use of quinidine in attempting to establish normal rhythm; and (3) after the irregular heart has been restored to normal rhythm.

It is the purpose of this paper to emphasize the importance and value of using both of these drugs for the most beneficial results in the treatment of auricular fibrillation.

FAGARINE—A NEW DRUG FOR THE TREATMENT OF AURICULAR FIBRILLATION AND FLUTTER

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Experimental studies made with fagarine have demonstrated that this drug increases the fibrillation and flutter threshold and can make auricular fibrillation disappear in the exposed heart.

Satisfactory results have been obtained in men with auricular fibrillation and auricular flutter of rheumatic, coronary, or hypertensive origin, with doses of fagarine between 0.08 and 0.10 Gm. administered in one dose by the intramuscular route. Some patients under the influence of digitalis have shown, however, some toxic symptoms.

The present study reports pharmacologic findings in experiments made in twenty-five normal individuals to whom the drug was administered in doses of

0.50, 0.60, 0.75, and 0.85 Gm. (1 centigram per kilogram of body weight) alone, or after atropine or complete digitalization.

Drug effects were studied clinically and electrocardiographically. No toxic symptoms were noticed. Electrocardiograms showed in all cases a definite increase of S-T interval with depression of this segment and of the T wave. These changes were proportional to the amount of drug employed. When atropine was given intravenously in doses of 1 mg., the electrocardiographic effects of fagarine were reduced in most of the cases. When fagarine was administered after the use of digitalis, in doses of 1 centigram per 5 kg. of body weight, the electrographic changes were accentuated.

Since fagarine in doses as small as 0.005 Gm. per kilogram of body weight has a definite effect on the heart muscle, it is concluded that a therapeutic assay should be started with this dose which is far below the toxic level. Special precautions should be taken in the case of patients who are under the influence of digitalis.

POST-TACHYCARDIA SYNDROME

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Certain cases of paroxysmal tachycardia deserve consideration because of clinical and electrocardiographic characteristics even though these cannot be explained upon an anatomic basis.

These characteristics, which make up the post-tachycardia syndrome, are as follows: (1) It is often seen in relatively young individuals without organic heart disease. (2) It is seen with prolonged and repeated bouts of paroxysmal tachycardia, commonly of ventricular origin. (3) Reversible cardiac enlargement occurs. (4) Depression of S-T, inversion and widening of the T wave, and prolongation of the Q-T interval, especially in Leads I, II, CR₄, CR₅, and CR₆, are recorded immediately after the attack or some hours later. (5) Electrocardiographic changes regress progressively over a period of several days. (6) Hypertrophy and dilatation of the heart with absence of any other important myocardial lesions are found at post-mortem examination.

Even though the post-tachycardia syndrome is not accompanied by histologic changes affecting the heart, it must not be considered harmless; death can occur suddenly from heart failure.

AURICULAR PREFIBRILLATION

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The authors report a study of sixty patients during the past nine years in whom there was a disturbance in auricular activity that preceded the onset of auricular fibrillation. A classification is proposed to describe auricular prefibrillatory disturbances. Prefibrillation P waves may be the only manifestation or they may be associated with: (1) auricular extrasystoles (of the common type, totally or partially blocked, isolated, or with short runs of tachycardia); (2) auricular tachycardia (paroxysmal, or of the common type, or atypical); (3) auricular "anarchy" and polymorphism of P waves; (4) auricular flutter.

Prefibrillation P waves show an alteration in height, width, or contour. Such changes may occur as an isolated or as a recurring phenomenon. Different morphologic types are described and are more important if found in the peripheral leads in patients with organic heart disease who have cardiac enlargement.

An auricular extrasystole acquires the characteristic of a prefibrillation disturbance if it occurs where prefibrillation P waves are present. Auricular extrasystoles frequently present varying degrees of block, the commonest being increase in the P-R interval. In some instances there are runs of auricular extrasystoles. Tracings are presented to show the importance of auricular extrasystole in determining the onset of auricular fibrillation.

Auricular tachycardia may be considered to be of (1) the common type and (2) the atypical type. These types may be recognized by the exceptional or the normal pattern of the P waves.

Polymorphism of the P wave is an intermediary degree between auricular extrasystole and auricular anarchy and is characterized by the presence (in the same tracing) of auricular waves with variable size and direction, and with irregular ventricular rhythm.

Auricular anarchy is defined as the greatest degree of polymorphism of the P waves. It is difficult to find the basic pattern. Clinical identification is impossible but complete arrhythmia exists and the electrocardiogram reveals that each ventricular complex is preceded (in a variable amount of time) by P waves of variable width, height, and form.

Auricular flutter is considered a prefibrillation form. The study of auricular prefibrillation shows disturbances of intraauricular conditions, auricular excitability, and hypertrophy of auricular muscle with distention or dilatation.

Experimental and clinical studies of the factors which lead to auricular fibrillation was purposely made in order to interpret the mechanism and significance of prefibrillation auricular disturbances. Several factors such as anoxemia, vagal action, auricular distention and dilatation, and structural lesions of the auricle were considered.

The conclusion is reached that the study of prefibrillation auricular disturbances gives support to the idea that auricular fibrillation is a result of irregular and multiple returning stimulations, having their origin in multiple premature auricular excitations with multiple regional and changing blocks.

Evolution and prognosis of prefibrillation auricular disturbances depend on (1) the type of disturbance, (2) the etiological factor involved, and (3) the efficiency of the treatment.

THE PATHOGENESIS AND TREATMENT OF HYPERTENSION

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Recent studies on experimental hypertension are reviewed in an attempt to evaluate the most likely hypothesis explaining the probable pathogenesis of chronic hypertension. The inadequacy of the pressor theory or renin hypothesis to explain the known facts is shown. An alternative hypothesis, in which the normal kidney is assumed to elaborate an essential metabolite in the organism, is in accord with the known experimental data. The application of these studies to the practical management of hypertensive cardiovascular disease is presented.

CRITICAL EXAMINATION OF THE CURRENT CLASSIFICATION OF THE LOCALIZATION OF MYOCARDIAL INFARCTS (THE AUTHOR'S TERMINOLOGY)

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Although it is generally accepted that infarction of the heart develops most often in the left ventricle, the author claims that the anatomicoclinical nomenclature proposed by him in 1936 makes it possible to localize the infarct more exactly. Furthermore, it makes possible a more accurate clinical and differential diagnosis, as well as prognosis. What has been described as infarction of the right ventricle is no more than an extension from the left ventricle caused by occlusion of that variety of left circumflex artery which has a distribution to the posterior wall of the right ventricle. This infarct is called the "anomalous type" (20 per cent of the cases).

A notorious confusion in the anatomicotopographic facts has resulted in many different names for infarcts according to their localization: for example, anteroapical; posterobasal; midventricular; undetermined; combined; atypical; anteroposterior; anterior, extensive; anteroseptal; anterolateral; laterobasal; posterolateral; posteroinferior; and multiple. On the contrary, the author states that according to his terminology the infarct is located in 80 per cent of the cases in the lateral, anterior, or posterior walls of the left ventricle, extending in some 20 per cent to the posterior wall of the right ventricle, but always being produced by the obliteration of branches of the left coronary system and never by obliteration of the right coronary artery.

The author attributes erroneous classifications to a disregard of the myocardial, pericardial, endocardial, and special conducting regions dependent on given arteries ("topographic myocardiovascular territories"). Upon such a basis and upon verification of anatomic, anatomicophysiologic, clinical, and electrocardiographic facts, the author was able to build up an anatomicoclinical nomenclature of infarction in the heart. This includes three syndromes which he names lateral, anterior, and posterior, depending, respectively, on obliteration of the left circumflex of short extension (not reaching the right ventricle), of the anterior descending or "normal type," and of the left circumflex of great extension or "anomalous type" (reaching the right ventricle). In referring to each syndrome, the author describes the pathologic changes, the symptoms, and the specific electrocardiographic patterns. Emphasis is also given to the mechanism of production and to the diagnostic, topographic, clinical, differential, and prognostic value of the systolic murmur, the pericardial friction rub, paroxysmal tachycardia with left ventricular extrasystoles, complete or incomplete auriculo-ventricular dissociation, right bundle branch block, partial left bundle branch block, and monophasic deviation of the S-T segment.

TREATMENT OF ACUTE CORONARY THROMBOSIS WITH DICUMAROL: FURTHER OBSERVATIONS

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The author has treated all private patients with acute coronary thrombosis seen by him between June, 1943, and June, 1946, with dicumarol in the hope of preventing thrombosing and embolic complications and thus reducing the death rate as well as lessening the morbidity. At the start of this therapeutic experiment it was hoped that the proper use of dicumarol would forestall the formation of mural (intracardiac) thrombi and subsequent embolic showers; the experience

thus far has confirmed this expectation. Added benefits of dicumarol treatment consist in the presumptive prevention both of extension of the initial coronary thrombus by propagation, as well as the formation of new thrombi in other coronary branches. (Multiple thrombosis is an intriguing phenomenon and its importance has been recognized in recent years without a satisfactory answer as to its causation.) Another important way in which dicumarol may benefit these patients is by preventing pulmonary embolism deriving from thrombosed veins in the legs and pelvis, since the majority of massive, fatal pulmonary emboli occurring in the course of acute coronary thrombosis have their origin in the deep veins rather than in the right ventricle.

A total of sixty-eight attacks occurring in sixty-two patients have been treated with dicumarol thus far, but the present report includes the data on forty-four patients reported last January by the author and his former associate, Dr. Samuel W. Page, Jr. Fifty of the group treated were 49 years of age or older with ages ranging from 38 to 81 years. There were forty-one men. The acute episodes were classed as severe forty-three times. There were thirty-eight first attacks, twenty-five second attacks, and five third attacks.

Results: There were eleven deaths, giving a mortality rate of 16 per cent, but since three patients expired before the prothrombin time could be altered significantly, it is justifiable to depict the mortality rate as 12 per cent of sixty-five attacks. In the thirty-eight first attacks, there was only one death, giving a mortality rate of less than three per cent in initial attacks.

Of the sixty-eight episodes studied, in only one was there any clinical evidence of pulmonary embolism after dicumarol therapy was started and this was not clear-cut, since the patient died in congestive failure and no autopsy was granted. Mesenteric artery embolism was found at autopsy in one patient, but the source was an atheromatous aortic plaque, since there was no mural thrombus present. No other systemic emboli were encountered clinically.

In none of the eight autopsied cases was there any evidence of mural thrombi, or pulmonary or systemic embolism (except for the instance in which the origin was in the atheromatous lesion). One patient, not autopsied, died from a cerebral accident which may have been hemorrhage, but he was found to be uremic shortly after dicumarol therapy was started and should not have received the drug, since renal impairment of severe degree is a contraindication. Another patient, a physician 81 years of age, who died fourteen days after beginning therapy, showed a ruptured left ventricle at autopsy with the usual intrapericardial hemorrhage. There was no evidence of undue hemorrhage or liver damage ascribable to dicumarol in the eight autopsied cases.

Peters and associates last April reported only two deaths in fifty patients similarly treated. This contrasted to thirteen deaths in a control group of sixty patients. Wright recently reported encouraging experiences in seventy-six similar patients given dicumarol. In both of these series, as well as in the present study, other common modalities of treatment were employed.

IMPORTANCE OF PRECORDIAL LEADS IN ELECTROCARDIOGRAMS AFTER EXERTION IN ANGINA PECTORIS; ACTION OF CERTAIN DRUGS (TRINITRIN, AMINOPHYLLINE, AND PAPAVERINE)

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The effects of exercise on the electrocardiogram were studied in sixty-four individuals. These included twenty-six normal persons, thirty patients with angina pectoris, and eight patients who had had cardiac infarction which was not followed by anginal episodes.

The following studies were made in every patient: (1) Leads I, II, and III, and precordial leads CF_1 , CF_2 , CF_3 , CF_4 , CF_5 , and CF_6 were recorded before and after exercise. (2) The behavior of blood pressure, the pulse rate, and the presence of subjective symptoms were observed during exertion. (3) The effect of certain drugs (trinitrine, aminophylline, and papaverine) upon the electrocardiogram before and after exertion and upon arterial blood pressure were observed.

None of the normal subjects showed a significant electrocardiographic response to exercise. In contrast, 80 per cent of the patients with angina pectoris showed a positive response. In 20 per cent of these positive reactors the change occurred in the precordial leads.

When deviation of S-T segment followed exercise, it was usually observed in Leads CF_1 , CF_2 , and CF_3 . When exercise produced inversion of the T wave as well as deviation of the S-T segment, this change was usually noted in Leads CF_3 , CF_4 , CF_5 , and CF_6 .

CARDIAC PAIN

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Cardiac pain is caused by a relative or absolute ischemia of a part or all of the myocardium.

The ischemia is caused by (1) great stress or overwork of the normal heart; (2) rapidly beating heart, as in hyperthyroidism, paroxysmal tachycardia, or auricular flutter; (3) impoverishment of the blood, as in anoxemia, anemia, or hypoglycemia; (4) disease of the coronary arteries; (5) myoplasia and anomalies of the coronary artery; and (6) spasm due to vagal reflexes.

Theories of cardiac pain, such as the stretching of the aorta, as held by Vacquez, and myocardial fatigue, as discussed by Mackenzie, are considered. Experimental evidence of diminished blood flow to the myocardium as the result of organic narrowing of a coronary artery or reflex spasm are critically examined. Cardiac pain is considered to be entirely the result of ischemia from the causes mentioned.

It is important for the clinician to differentiate the causes of cardiac pain: (1) Cardiac pain resulting from coronary artery sclerosis depends on other evidence of arteriosclerosis, especially electrocardiographic changes. (2) Pain as the result of artery spasm is usually reflex from the lung or abdominal viscera. Vagal reflex spasm is relieved or diminished by full doses of atropine. (3) The radicular syndrome from lesions of the lower cervical or upper dorsal vertebrae may simulate anginal pain very closely.

HERNIA OF ESOPHAGEAL-HIATUS: ITS RELATIONSHIP TO ANGINA PECTORIS

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1. One hundred private patients in whom a diagnosis of angina pectoris had been made were studied by x-ray to determine the presence of hernia of the esophageal hiatus. Twenty-five such hernias were found, twenty-two of the small type and three of the large type.

2. Six of this group of twenty-five patients with hiatus hernia had the symptoms relieved by medical management. A seventh, with a typical picture of angina pectoris, was relieved of all symptoms following surgical repair of a large hiatus hernia.

3. One patient, followed for a period of fourteen years, had probably a hiatus hernia at first and added coronary disease later. This instance is cited to emphasize the point that both conditions may occur together.

4. Another patient, complaining of pain beneath the lower third of the sternum radiating to the left shoulder, had a large hiatus hernia 9 cm. in diameter and a hemoglobin of 46 per cent. Bleeding points or ulceration within the hiatus hernia have been recorded in 11 per cent of one group of patients reported in the literature. In such instances correction of the anemia often relieves the symptoms.

5. A control group of 957 patients who received x-ray study of the gastrointestinal tract, in which a search for hernia of the esophageal hiatus was a routine part of the procedure, were found to have hiatus hernia to the number of seventy-eight, or 12.27 per cent. The highest incidence reported in any other control group is 3 per cent.

RESULTS OF SURGERY IN PATENT DUCTUS ARTERIOSUS

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1. An analysis of 643 patients who underwent operations for patent ductus arteriosus by forty-six surgeons has been presented.

2. Six hundred twenty-six individuals were found to have a patent ductus at operation, 525 were uninfected and 101 were infected. In seventeen instances the diagnosis was incorrect.

3. The mortality rate in ligation of the uninfected duct was 4.9 per cent. However, 8.7 per cent resulted in recanalization.

4. Ligation of the duct is now obsolete and should be done only where section is impossible. That section of the duct is a safe and practical procedure is established by the fact that 172 patients with uninfected patent ductus arteriosus have been so treated without a single fatality and no recanalization.

5. Errors in diagnosis will be less frequent if only patients with the typical machinery murmur are subjected to surgery.

THE DIFFERENTIAL DIAGNOSIS OF AORTIC STENOSIS, PULMONARY STENOSIS, PATENT DUCTUS ARTERIOSUS, AND COARCTATION OF THE AORTA

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The purpose of this paper is to discuss the differential diagnosis of the following clinical conditions involving the cardiovascular system: (1) aortic stenosis, (2) pulmonary stenosis, (3) patent ductus arteriosus, and (4) coarctation of the aorta.

Clinical diagnosis of these states is now possible if one takes into account the location and the timing (time relationships) of the thrills and murmurs with respect to the first sound at the apex. This can be done by using the symballophone which makes it possible to compare the time of appearance of two sounds of similar or dissimilar qualities.

Thrills and murmurs originating in the circulatory system travel in both directions, but travel a greater distance in the direction of the blood flow. They travel peripherally on the pulse wave; the rate at which they progress is determined by the level of the diastolic pressure. Roughly, the waves travel at the rate of 10 to 15 meters per second, which increases as the pulse wave approaches

the periphery in the arterial system. If the thrills and murmurs travelled as sound waves, they would travel from 100 to 200 times as fast as they actually travel.

Aortic Stenosis.—The systolic thrill and murmur are located adjacent to the right border of the sternum and at that point are synchronous with the first sound. They are propagated along the course of the aorta and great vessels of the systemic circuit. They appear later than the apex impulse and the first sound at the apex, and the greater the distance from the heart, the greater the delay in time of appearance. They can be shown to be synchronous with the pulse wave.

Pulmonary Stenosis.—The systolic murmur is found adjacent to the sternum on the left in the second intercostal space. It is synchronous with the first sound and is not transmitted beyond the thorax. Its pathway follows the pulmonary artery. Its intensity is more marked in the upper part of the chest on the left because the left pulmonary artery is more superficial than the right branch, which lies behind the ascending limb of the thoracic aorta. If one compares the timing of the systolic murmur at some point distant from the pulmonary valve with the first sound, its appearance will be somewhat later than the first sound.

Patent Ductus Arteriosus.—This congenital anomaly generally shows the characteristic continuous murmur with the so-called "systolic accentuation." The thrill and the accentuated phase of the murmur are found in the same location as in pulmonary stenosis, but they appear much later than the first sound at the apex, because the pulse wave must pass through the ascending limb and arch of the thoracic aorta and through the ductus arteriosus before the accentuated phase is produced. This delay in timing is sufficient to establish the diagnosis.

Coarctation of the Aorta.—The so-called "systolic murmur" is heard in the upper dorsal thoracic region adjacent to the spine. The murmur actually is not produced until the pulse wave in the thoracic aorta has reached the narrowed channel at the site of coarctation. Therefore, the difference in timing with the first sound at the apex is notable and can be determined easily by the methods discussed.

REPORT OF A CASE OF TRICUSPID INSUFFICIENCY OF THE EBSTEIN TYPE WITH PROBABLE FETAL ENDOCARDITIS AND EXCEPTIONAL ELECTROCARDIOGRAPHIC CHARACTERISTICS

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The nineteenth case of tricuspid insufficiency of Ebstein's type is reported. It has as special features fetal endocarditis caused by rheumatic fever of the mother during pregnancy and an electrocardiogram with retrograde P waves following the initial ventricular deflections. It is concluded that the defects observed were developmental in origin and that the valvulitis was superimposed. The electrocardiographic features are explained on the basis of a retrograde activation of the auricles through the intimal union between leaflets of the tricuspid valve and the ventricular wall.

CLASSIFICATION OF CONGENITAL HEART DISEASES

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The authors have made a critical study of the different classifications of congenital heart disease from those of Pezzi and Laubry up to that of Cossio. The clinical, angiocardigraphic, and anatomicopathologic analysis of the author's material from 1935 forms the basis for a new classification that takes account of previous work on the subject and tries to avoid former errors and omissions, which are to be explained by lack of the resources of modern methods of clinical investigation that the cardiologist now possesses. It is the purpose of this new classification to facilitate the task of clinicians, pediatricians, cardiologists and radiologists in diagnosis.

There is used for the first time in medical literature the word "biologia," meaning the association of two congenital defects, such as pulmonary stenosis or atresia with interventricular communication, or association of the latter with interauricular communication. In the first example, pulmonary stenosis with interventricular communication, the authors establish three degrees of biologia: type I, type II, and type III.

The authors introduce in the subgroups microcardia, formerly neglected, and the abnormalities of the vena cava. They also point out that agenesis of some of the branches of the pulmonary artery, such as are found in lack of development of the lung, are to be considered in the classification.

It is stated that this classification has as its basis not only clinical and electrocardiographic findings, but also the findings revealed by angiocardigraphy and the data obtained in post-mortem examinations.

Angiocardigraphic technique has permitted the correction of many diagnoses that would have been made incorrectly if there were taken into consideration only the findings revealed by the usual clinical methods.

CARDIAC FAILURE IN TRICUSPID DISEASE

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The author studied nine patients with rheumatic disease with involvement of the tricuspid and the mitral valves, with the aim of investigating the fundamental cause of the dyspnea. The following tests were performed in each case: lung ventilation, lung volume and its divisions, alveolar air, oxygen consumption, oxygen difference between arterial and venous blood, blood velocity, and blood volume.

The following results were obtained: Minute output was found normal in all patients without heart failure and was lessened in patients with heart failure. As is seen in other forms of heart disease, the diminution of the minute output corresponded to the degree of cardiac failure. Blood volume was increased in all patients, even in the absence of cardiac failure. Lung ventilation was augmented in most patients in proportion to the degree of cardiac failure. Oxygen consumption proved to be above the normal level. Oxygen and carbon dioxide equivalents were found diminished in relation to hyperventilation and increase in oxygen intake. Vital as well as total lung capacity was decreased; residual air remained within normal limits. No correspondence was found between venous pressure or blood velocity or arteriovenous oxygen difference

and lung ventilation. On the contrary, it was observed that the respiratory changes in tricuspid disease are comparable to those known to occur in mitral involvement.

It is therefore concluded that dyspnea in tricuspid disease of rheumatic origin has to be attributed mainly to the coexistence of mitral pathology.

A NEW DIAGNOSTIC SIGN OF TRICUSPID INSUFFICIENCY

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Post-mortem studies made at the Instituto Nacional de Cardiología de Mexico have shown that the incidence of real tricuspid insufficiency with functional disturbance is 33.3 per cent, and that the incidence of functional insufficiency is 5.44 per cent, a total incidence of 39 per cent.

Since valvular lesions of the tricuspid valve are difficult to diagnose, a new sign that may facilitate the clinical diagnosis of tricuspid insufficiency is described.

The new sign consists in producing a tricuspid murmur in patients in whom no murmur is heard, or in increasing the intensity of a previously heard murmur by having the patient take a deep inspiration or hold his breath after a deep inspiration. A very short period of apnea such as occurs when children cry may be enough to make the acoustic change noticeable. In some patients the characteristic murmur can be noticed during normal inspiration. The increased intensity of the murmur may or may not be associated with changes in pitch. The intensity is almost always increased; in some patients, however, the murmur does not change in intensity. Even when the intensity is not increased, the sign is of value since the intensity of other cardiac murmurs may be diminished by the procedure. The site of maximum intensity of the tricuspid murmur is usually the tricuspid area, but the site may be changed either to the right or left of the sternal bone; there were cases recorded in which the murmur was heard loudest close to the apex.

The new sign seems to be present in 90 per cent of patients with tricuspid insufficiency. The new sign is considered to be rarely absent in proved cases of tricuspid insufficiency.

EXPERIMENTAL STENOSIS OF THE PULMONARY ARTERY

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Stenosis of the pulmonary artery was surgically produced which reduced the lumen of the vessel at least 50 per cent. Hypertension of the corresponding territory followed the operation and aortic and pulmonary blood pressures were recorded with a Hamilton manometer during the operation, and changes in pressure that developed after operation in the pulmonary and general circulation were followed. The effects of the hypertension on the weight of both ventricles and the diameter of the myocardial fibers were studied. To accomplish the latter study, a small piece of muscle was removed at the first operation.

ANGIOGRAPHY OF THE AORTA

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A new method of arteriography of the thoracic aorta has been successfully used by the authors. Good roentgenograms of the thoracic aorta, its main branches, the arteries of the neck, and the coronary vessels were obtained by means of direct injection of opaque solutions into the aortic arch.

BENIGN RESIDUAL ARRHYTHMIAS

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Two fundamental observations have led the authors to describe the so-called benign residual arrhythmias. The first was the appearance of coupled ventricular extrasystoles during the course of a severe attack of influenza in a woman 30 years of age, who was known before this illness to be normal from the cardiologic standpoint. Although the infectious disease disappeared, the disturbance in rhythm has persisted without change for fifteen years, without any other manifestation of heart disease.

The second observation was the appearance of second degree A-V heart block in four young persons who had been under observation for a long period of time (two to fifteen years); in these individuals the arrhythmia has been the only expression of cardiac abnormality. Search for etiological factors was carefully made without any result, and the evolution of the disturbance has shown it to be harmless.

From these observations the conclusion has been reached that there exists a group of arrhythmias which are of benign character. The different types of arrhythmias belonging to this category are the following: ventricular and auricular extrasystoles; bigeminal ventricular extrasystoles; simple increase in the conduction time; temporary A-V block and other forms of incomplete A-V block; intraventricular blocks; and paroxysmal auricular fibrillation (present in one patient for twenty years).

Reference is made to the frequency with which some infectious or parasitic diseases produce myocardial lesions. It is suspected that many disturbances of the cardiac system of unknown cause, including the benign arrhythmias that have been referred to, have their origin in inactive fibrous scars left by old myocarditis. In myocarditis total recovery may occur, or in the case of necrobiosis, scar tissue can be formed with areas of interstitial fibrosis that may constitute a definite obstacle for the conduction of the stimulus, or a permanent factor of irritation. The fibrous lesions, a result of acute inflammatory changes affecting the heart muscle, have been very well known to pathologists for a long time, but their presence has been ignored by clinicians.

Knowledge of residual benign arrhythmias has a very useful value from the practical standpoint, because their prognosis is excellent, there is no tendency to progression, and there is little or no response to therapeutic measures. The patients with benign residual arrhythmias have very few or no symptoms, and in many cases the arrhythmia is discovered during routine medical examinations. The authors believe, therefore, that physicians must take into consideration this disturbance which is benign but which probably has a definite pathologic cause.

BUNDLE BRANCH BLOCK: A REVIEW OF 100 CASES

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A study has been made of 100 cases of bundle branch block occurring in a total of 6,900 patients, who received an electrocardiographic examination at the U. S. Naval Hospital, Long Beach, Calif. Only cases demonstrating a QRS duration of 0.2 second or more and indicating in the precordial leads asynchronous activation of the ventricles were selected.

In the survey there were twenty-eight patients under 40 years of age, including seven under 20 years. Twenty-nine patients revealed no apparent organic heart disease as determined by the cardiac history and physical, laboratory, and x-ray examinations. Thirteen of these twenty-nine cases, or 44 per cent of the "no apparent disease" group, were under 40 years of age. Of the group of twenty-nine with no apparent disease, eighteen had a wide "S" wave pattern of bundle branch block; six (33 per cent) of the eighteen were under 40 years of age.

The identification of etiology revealed that the largest single group, thirty-five patients, had coronary heart disease, of which eighteen presented evidence of myocardial infarction. There were eighteen individuals with hypertensive heart disease. The balance of the patients were included in a miscellaneous group consisting of rheumatic, syphilitic, congenital, and infectious heart disease. The two patients who comprised the group of infectious heart disease had mumps and diphtheritic myocarditis; both patients survived.

The classification of the bundle branch block was based upon the multiple precordial leads. There were forty-four cases of right bundle branch block with a delay in the intrinsic deflection presenting an M shaped QRS pattern in the precordial leads over the right side of the heart. Thirty-nine cases had a delay in the intrinsic deflection presenting a M shaped QRS pattern in the precordial leads over the left side of the heart characteristic of left bundle branch block. The remainder of the series was unclassified because the precordial leads from both the lateral sides of the heart were not available. Of the thirty-nine patients with left bundle branch block, eight had a Q wave in the first standard lead, and five of the latter eight had myocardial infarcts.

Six patients, two with no apparent heart disease, have had a known bundle branch block for periods ranging from eight to nineteen years. Four of these have a wide S pattern.

It is concluded that bundle branch block is not uncommon, that it occurs more frequently in the younger age group than was formerly believed, and that many of the individuals with this abnormality present no evidence of organic heart disease. This series supports the present opinion concerning the more favorable prognosis in those patients having the wide S pattern. The generally accepted grave prognosis associated with all types of bundle branch block must be modified in view of the existing cases of block occurring in individuals without apparent heart disease and of the increasing number of cases reported of patients who have heart disease and have had bundle branch block for over ten years.

ELECTROCARDIOGRAPHIC STUDIES IN PUERTO RICO WITH UNIPOLAR PRECORDIAL LEADS IN NORMAL INDIVIDUALS OF BOTH SEXES AND AT DIFFERENT AGES

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The author presents the last of four reports based on the study of the unipolar electrocardiograms made in 161 normal Puerto Rican natives of both sexes between 5 and 46 years of age. Previous communications dealt with T waves as found in precordial leads, pulse frequency, anatomic position of the heart and \bar{A}_{QRS} , and the unipolar potentials of the extremities. The present report deals with the results obtained by using the precordial leads in the same group of individuals.

Previous studies of the precordial leads in normal persons have been made on adults and infants. No reports have been found in medical literature on the precordial leads in normal persons from 15 to 18 years of age.

The following are the most important findings: (1) The S-T interval was frequently found to be slightly elevated (not more than 1.5 millimeters). The single instance of S-T depression was recorded in V_6 in a man. (2) The P wave had a duration of as much as 0.12 second in only one woman, in V_3 , V_4 , and V_5 . (3) The P-R interval did not exceed 0.22 second. (4) The duration of the QRS complex was as great as 0.12 second in one man, in V_5 , and in one woman, in V_1 and V_2 . (5) R-T interval was found between 0.24 and 0.44 second, with an average of 0.32 second. (6) P was of a low voltage in leads taken from the right, and inconspicuous or flattened in leads taken from the left precordium. (7) Q was absent in V_1 , V_2 , and V_3 . (8) The R wave increased in amplitude progressively from V_1 to V_5 . In a man the lowest R wave was found in V_1 ; in a woman, in V_4 and V_5 . In both sexes the highest R wave, on an average, was found in V_5 . (9) S waves were prominent in V_1 , increased in amplitude in V_2 , and then diminished in amplitude progressively to V_6 . (10) The T wave varied considerably; in children of both sexes, 5 to 11 years of age, this wave may be negative in V_1 , V_2 , V_3 , V_4 , and perhaps in V_5 ; in youngsters and in women, in V_1 , V_2 , and V_3 ; and in men only in V_1 . (10) A U wave occurred more frequently in adults than in adolescents and children. In all age groups the incidence of U waves was a little more in women than in men.

CONCEALED A-V CONDUCTION: THE EFFECT OF BLOCKED IMPULSES ON THE FORMATION AND CONDUCTION OF SUBSEQUENT IMPULSES

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1. The spread of an impulse which affects the A-V junction by penetrating into it without traversing it, thus failing to reach the auricles or ventricles (depending on the direction in which the impulse travels), finds no direct expression in the electrocardiogram. Indirect evidence of such concealed A-V conduction is the influence of the blocked impulse on the transmission time or on the formation of a subsequent impulse.

2. The literature dealing with the effect of blocked impulses on conduction and formation of subsequent impulses is reviewed. (a) The simplest example of the effect of a blocked impulse is the postextrasystolic P-R prolongation due to blocked retrograde conduction after an interpolated ventricular premature systole. (b) Similarly, the failure of the sinus impulse following a ventricular premature systole to elicit a ventricular response may be due, in some instances, to the inability of the A-V junctional tissues to transmit the impulse

after it has been affected by the blocked retrograde impulse of the ventricular premature systole, and not to refractoriness of the ventricular muscle. (c) The pause after ventricular premature systoles in the presence of auricular fibrillation indicates that a retrograde impulse has affected the junctional tissues. (d) The increase in the grade of a partial A-V block following ventricular premature systoles, even if they are not followed by a retrograde P, demonstrates the effect of blocked retrograde impulses. (e) Cases of complete forward block in the A-V junction and preserved retrograde response show the effect of the blocked forward impulse on subsequent retrograde conduction. (f) A blocked retrograde impulse, by reaching a depressed area in the A-V junction prematurely, may prolong the period of rest in that area and thus shorten the conduction time of the subsequent forward impulse. (g) It is conceivable that in depressed cardiac muscle an impulse, falling into the supernormal phase of a preceding blocked impulse, may be conducted faster instead of being delayed by the effect of the blocked impulse. (h) Multiple blockage may occur as a result of a blocked impulse which was partially conducted and which influenced the subsequent impulse in the same way as a completely conducted one; such a mechanism is probably common in auricular flutter. (i) A blocked A-V nodal premature systole may account for a "dropped beat," and a blocked and interpolated nodal premature systole can give rise to an apparently unexplained P-R prolongation of a single beat. (j) In cases of A-V dissociation some of the impulses of the slower pacemaker (S-A node), after passing and discharging the faster A-V nodal pacemaker, may be stopped below the latter before reaching the ventricles. The result of such concealed A-V conduction is a disturbance in the impulse formation of the nodal pacemaker.

3. Three new instances demonstrating the effect of blocked A-V impulses on succeeding impulse conduction, and one showing the influence on subsequent impulse formation, are reported and illustrated. They demonstrate: (a) the effect of a blocked auricular premature systole on A-V conduction of a subsequent auricular premature systole from the same focus; (b) the effect of the blocked auricular impulses on subsequent A-V conduction in a case of 2:1 A-V block, depending on the exact position of the blocked P wave in the cardiac cycle, thus confirming the existence of a "phase of interference" and explaining the transition from one grade of block to another; (c) the effect of the blocked flutter impulses in a case of auricular flutter with 2:1 A-V conduction giving rise to a pseudo-alternans of A-V conduction; and (d) a hitherto unreported disturbance of impulse formation, that is, discharge of the A-V nodal pacemaker by blocked reciprocal beats.

4. These observations support the view that concealed A-V conduction may account for the difficulty in analyzing some curves of auricular flutter with a varying ratio of A-V conduction. The same phenomenon may also explain some of the discrepancies encountered in the construction of recovery curves of A-V conduction in cases of partial A-V block based on simple correlation of the P-R and R-P intervals.

SINOAURICULAR BLOCK

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The authors report fifteen cases of proved sinoauricular block and review the evolution of the presently accepted ideas on this subject. They emphasize their agreement with the conclusion of Vidoya, González Videla, and Aguiar. The classification of complete and incomplete block is accepted. Complete sinoauricular block is divided as follows; (1) simple increase in sinoauricular conduc-

tion time, (2) progressive increase with auricular failure, and (3) progressive increase without auricular failure. Complete block may provoke diastolic standstill or shift of the pacemaker to an idioventricular center.

Incomplete block may be of minimal degree and escape detection. Periodic sinus arrhythmia is a frequent form of this type of block, but little has been written on the subject. The authors refer to sinus standstill as sinus abortion, and hold the opinion that this is a true sinoauricular block. An analysis is made of complex forms of sinoauricular block influenced by the activity of secondary centers.

In the cases studied the following causes for a sinoauricular block were recognized; (1) vagotonic state, (2) arteriosclerotic heart disease, and (3) digitalis poisoning. The prognosis and treatment of sinoauricular block is discussed.

ARTERIAL HYPERTENSION—ITS MEDICAL AND SURGICAL ASPECTS

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1. Renal arteriosclerosis is the first step in the development of elevation of blood pressure. Arterial constriction (renal ischemia, Goldblatt's phenomenon) plays a paramount role in the production of arterial hypertension.

2. Page and co-workers in North America and Houssay in Argentina, have elaborated the theory of an enzyme called renin as a causative agent of arterial hypertension. This substance is normally secreted by the kidneys into the circulatory system. The combination of renin and hypertensinogen (a pseudoglobulin substance formed in the liver), or renin activator as it is also called, produces Page's angiotonin or Houssay's hypertensin. These substances circulating in the blood stream determine arterial constriction and, consequently, arterial hypertension.

3. The existence of a substance called hypertensinase has also been demonstrated by Argentine workers. This is normally produced in the kidneys and its function is to neutralize the hypertensive action of hypertensin. This substance may be responsible for the hypotensive effects of renal extracts.

4. Surgical procedures are useful in a number of cases. Vitamin A, renal extracts, and thiocyanate are the drugs most widely employed at the present time.

5. In 1932, Dr. Domingo H. Gomez Gimeranez of Cuba suggested the existence of a hypotensive and urolytic substance which is normally produced in the cortex of kidneys, and which has been named Nephreptine by the author.

RETINAL ANGIOSCOPY IN ESSENTIAL ARTERIAL HYPERTENSION (A STUDY OF 300 CLINICAL CASES)

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The pathogenesis, nature, and clinical significance of fundus changes in essential hypertension are still obscure. Clarification was sought by (1) a statistical study of the incidence of retinal changes; (2) their correlation with systemic symptoms; and (3) a correlation of the retinal changes with the data from the general clinical study (arterial tension values, large vessels status, cardiac, and renal function, etc.).

Clinical Material.—Three hundred patients with essential arterial hypertension have been studied. These were chosen at random from a group of 790 patients examined during the last two years at the National Institute of Cardiology.

Method.—The fundus modifications, the systemic changes, and the laboratory data have been tabulated. Statistical studies of the fundus modifications and the modifications of the general state have been made. The percentage and the corrected arithmetical mean with the calculation of the standard deviation and the coefficient of variation were computed in each patient. These quantitative data have been presented in graphic form.

Conclusions.—

1. The two kinds of retinal arterial narrowing in essential hypertension, that is, uniform narrowing and localized constrictions, are probably two different phenomena and not simply two ophthalmoscopic variations of the same phenomenon. This opinion is supported by the failure of both changes to occur frequently in the same eye; by the lack of parallelism in the intensity of the reaction when both co-exist in the same eye; and by the evident relationship of localized constrictions to the diastolic blood pressure, lesions of the retinal parenchyma, and cardiac and renal insufficiency.

2. The evidence indicates that uniform narrowing is a manifestation in the retina of tonic arteriolar contraction of humoral origin, and that localized constriction represents spasm from a superimposed action of the vasomotor nerves.

3. The primary phenomenon in the fundus of hypertensive patients is the tonic contraction of the retinal arterioles. We must recognize, however, that, taking the group of patients as a whole, this contraction is slight and that although it increases when the diastolic pressure rises, it does not bear any direct relationship to it.

4. Uniform narrowing has a proportional relationship to sclerosis of the retinal small arteries, which confirms the opinion that tonic contraction is the pre-existing phenomenon in the ocular circulatory system.

5. Vascular spasm is related to lesions of the retinal parenchyma and to cardiac and renal insufficiency. This confirms its significance as a sign of "activity" and its importance as a prognostic aid.

6. The existence of retinal vascular sclerosis in a hypertensive patient does not imply the existence of aortic sclerosis, but the statistical data show that it may suggest the presence of associated sclerosis of the coronary system.

7. The papilloretinal edematous lesions (edema, cotton-wool patches, detachment of the retina, and choked disc) and the nonedematous lesions (shiny patches) are quantitatively related in our statistics with the degree of cardiac and renal insufficiency. The first type is a manifestation of "activity" or progression of the hypertension, and the second type is a manifestation of an old established process. The identification of one or the other type of involvement indicates in a general way whether the cardiac muscle and the renal parenchyma have been harmed by a rapidly or a slowly developing process.

8. The variations in the caliber, degree of spasm, and amount of sclerosis of the retinal arterioles in hypertensive patients with retinopathy reflect a peripheral circulatory determinant and are not the result of noxious action of supposed toxic products retained by insufficient renal elimination.

9. The author points out that the high values of the standard deviation and the coefficient of variation which frequently accompany the arithmetical mean show how widely scattered are the individual values around the mean. The degree of the fundus changes in hypertensive patients is not always proportional to the clinical state. This reflects the variability in the evolution of the disease. Although Page and Corcoran insist that the ophthalmoscopic examination continues to be the most useful method "to discover the grade and the severity of vascular deterioration in a hypertensive patient," excessive caution is to be used in applying deductions which are valid from a general point of view to every patient.

VALUE OF THE PRESSOR TEST IN HIGH BLOOD PRESSURE

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Comparative studies were made in 100 patients with high blood pressure by using the cold pressor test after the technique of Hines and Brown, and the Taquini and Garcia Campo test, consisting in the intravenous injection of 0.025 Gm. of efetonine. The patients belonged to types I, II, and III of the classification of Keith, Wagener, and Barker. Ten patients had symptoms of hypertensive heart disease. In six individuals determinations were made of the minute-volume flow with four samples, following the Grollman technique.

In patients belonging to type I, the response to cold varied between 8 and 60 mm. Hg, with an average value of 24.2; Efetonine gave a response of between 16 and 72 mm. Hg, with an average of 31.4. In patients belonging to type II, the response to cold was between 12 and 60 mm. Hg, with an average value of 31; efetonine gave a response between 20 and 80 mm. Hg, with an average of 42.7. In the patients of type III cold gave a response between 20 and 70 mm. Hg, with an average value of 37.8; with efetonine the figures were between 28 and 72 mm., with an average value of 51.4. In ten patients with hypertensive heart disease the highest response to cold was 22 mm. Hg, the lowest was 2 mm. and the average of all the group was 11.7; responses to efetonine were between 8.28 and 22.1 mm. Hg, respectively.

Both tests showed a relationship to the basal blood pressure but not to the maximal variation or the variability of the blood pressure.

The determinations of the minute-volume and the correlated functions during the cold pressor test showed that there was an increase in the use of oxygen of between 6.7 and 33.8 per cent. The minute-volume flow in general was parallel to the oxygen consumption. The difference of the oxygen content in arteries and veins was maintained without significant variation. The studies made with efetonine showed an increase of between 16.5 and 46.1 per cent in the use of oxygen. The minute-volume was also found to be increased between 53.8 and 100.2 per cent. This relatively higher increase of the minute-volume in relation to the use of oxygen was accompanied by a decrease of the arterio-venous oxygen difference varying between 9.6 and 35.4 per cent.

It is concluded that the variations in the minute-volume, the hemodynamic factors caused by a high blood pressure, and the organic changes in the vascular system may explain the differences observed between the cold pressor and efetonine tests. It is pointed out that these factors have to be taken into consideration when deductions concerning the vasomotor reactivity of hypertensive patients are based upon the results of the pressor tests.

THE ROLE OF SURGICAL TREATMENT IN THE
MANAGEMENT OF HYPERTENSION

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The discovery of hypertension in a patient fixes a responsibility; a chronic disease henceforth must be managed systematically and scientifically. It is necessary to be on the alert for evidences of activity and progression of the hypertensive state. Such manifestations constitute the indication for surgical treatment. Splanchnic resection has proved capable of arresting, and sometimes reversing,

the progressive deterioration of arterial hypertension in a significant percentage of patients. The earlier the evidences of progressive hypertensive disease are recognized and splachnicectomy is performed, the more likely are the results of surgical treatment to be beneficial.

EXPERIENCES IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN

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Twenty-two patients with subacute bacterial endocarditis were treated with penicillin given in long courses and in large doses. Cure was achieved in twenty patients (in twelve patients cure has endured from one to two and one-half years thus far). One patient had a return of the disease within two months of treatment, and another patient suffered a reinfection six months after her original cure; both patients were again cured.

The underlying heart disease was congenital in two cases and rheumatic in the others. The patients ranged in age from 3 to 65 years. None of the survivors are invalids.

The infection was due to *Streptococcus viridans* in each case. The penicillin resistance of the infecting organism ranged from 0.01 to 0.05 units per cubic centimeter of culture required to inhibit growth in vitro.

Four methods of penicillin administration were tested: (1) intramuscular injections at two-hour intervals, (2) continuous intramuscular infusion-drip, (3) continuous intravenous infusion-drip, and (4) one or two daily intramuscular deposits of massive doses of penicillin in an oil and beewax medium. Serum penicillin concentrations with each mode of treatment indicated the superiority of the continuous intravenous and of the intramuscular deposit (in oil and beewax) methods for maintaining sustained penicillin concentration in the blood.

The total amounts of penicillin administered in the cured patients ranged from 3,900,000 to 102,000,000 units, and the duration of treatment ranged from three weeks to seventeen months.

In one cured patient, who died nine months later of another disease, the fibrocalcific, sterile, and abacterial lesion of the previous endocarditis which was seen at necropsy proved anatomically that the infection had been eradicated.

Representative cases were presented briefly and were illustrated by projected charts.

PENICILLIN IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS: FURTHER STUDIES IN TWENTY-ONE PATIENTS

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The author reports the results of treatment of twenty-one patients with subacute bacterial endocarditis by the use of penicillin. The patients were divided into two groups according to the methods of treatment as follows: the first group included nine individuals who were treated by different physicians, using different methods of administration of the drug; the second group was composed of twelve patients whom the author treated according to a relatively uniform method.

The time of evolution of the disease, the general state of the patient, and sensitivity of the isolated streptococcus to penicillin were alike in both groups.

Penicillin was administered to all patients by the fractionated intravascular method; injections were given at first every three hours and later every two hours. The author stresses that the aim of any method, regardless of the particular procedure employed, is to maintain the highest penicillin blood levels.

The first group of patients received from 160,000 to 240,000 Oxford units of penicillin, the second group received from 160,000 up to 2,000,000 Oxford units daily. The average total dose was 11.5 million units in the first group and 22.5 million units in the second group of patients. Treatment was given over a period of six to seven weeks; heparin was used in three cases of the first group and in none in the second. Other therapeutic measures (iron, vitamins, blood transfusions, etc.) were used in the patients of both groups.

The following results were obtained: In the first group eight patients died and one was cured (11.1 per cent cured); in the second group there were four deaths and eight cures (66.6 per cent of the cases were cured).

These figures stress the necessity of employing high doses of penicillin. It is to be expected that the author's statistics will give better results in the future since he now systematically employs large doses of penicillin, 1.2 million units daily with a total dose of 50 million units per patient.

PULMONARY EMBOLISM IN MEDICAL PATIENTS: A COMPARISON OF INCIDENCE, DIAGNOSIS, AND THE EFFECTS OF TREATMENT OF 273 CASES AT THE MASSACHUSETTS GENERAL HOSPITAL IN TWO FIVE-YEAR PERIODS (1936 TO 1940 AND 1941 TO 1945 INCLUSIVE)

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An analysis has been made of the incidence, symptoms and signs, and treatment of pulmonary embolism in medical patients at the Massachusetts General Hospital during two five-year periods, from 1936 to 1940 inclusive (Group A) and from 1941 through 1945 (Group B). During the entire ten years the ratio of patients with pulmonary embolism on the medical wards (0.6 per cent) was more than twice that of patients on the surgical wards (0.24 per cent). Although there were actually more than twice as many surgical cases (98,642) as medical (45,523), more than half (53.4 per cent) of all the patients with pulmonary embolism were medical (273 as compared to 238 surgical). Of the 273 medical cases with pulmonary embolism, 122 were diagnosed during the first five years and 151 during the second, due at least in part to an improvement in diagnostic ability.

Males predominated, making up 56.5 per cent in Group A and 60.3 per cent in Group B. The great majority of the patients were over 40 years of age (83.8 per cent) and over one-half were from 50 to 70 years of age. The majority of the patients had cardiac disease (59 per cent in Group A and 70.8 per cent in Group B). All kinds of heart disease were represented, especially the rheumatic, hypertensive, and coronary forms. Congestive failure was frequent as a background and auricular fibrillation was present in nearly one-third of the patients.

Of the symptoms, chest (mostly pleural) pain was the most common but not the earliest, being found in about one-half the patients (49.1 and 56.9 per cent in the two groups cited). Dyspnea was present in one-third (31.9 and 35.7 per cent), but hemoptysis occurred in a relatively small group (10.4 and 18.5 per cent). Tachycardia out of proportion to the degree of fever or dyspnea was a

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prominent sign. Physical abnormalities in the chest were often absent; a pleural friction rub was found in less than 10 per cent of the patients (9.8 and 8.6 per cent). The roentgenologic diagnosis of pulmonary infarction improved considerably in the second five-year period as compared with that in the first (57 and 33 per cent). The electrocardiographic pattern of acute cor pulmonale was evident in about one-fifth of the patients electrocardiographed.

Autopsies in ninety (72 per cent) of the 125 patients who died showed massive embolism in 50 per cent. In only a few cases (twelve) were thrombi found in the right heart chambers. Over 75 per cent of those whose leg veins were examined showed thrombosis therein.

In only one patient during the first five-year period were the femoral veins interrupted, but in the second period the operation was done bilaterally on either the superficial or common femoral veins (the latter are the preferable site) in sixty patients with a reduction of early mortality (within one month) to 28.3 per cent as compared with 50.7 per cent in those without operation.

The possibility of pulmonary embolism in medical patients, especially in those with cardiac disease, should be constantly borne in mind and treated prophylactically by bilateral common femoral vein interruption when discovered.

CARDIAC ASTHMA AND ACUTE EDEMA OF THE LUNGS IN MITRAL STENOSIS WITH AURICULAR FIBRILLATION

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The authors studied fifty-one patients with mitral stenosis or mitral disease with paroxysmal dyspnea. In twenty-one (two with arterial hypertension and five with aortic valvular disease) the rhythm was of sinus origin. In eight of the thirteen patients with auricular fibrillation and normal blood pressure, the abnormal auricular rhythm existed before the onset of cardiac asthma and acute edema of the lung. Thus, acute auricular insufficiency was not the cause of these pulmonary phenomena in these patients.

The more probable factors determining the sudden pulmonary stasis in mitral stenosis with or without auricular fibrillation appear to be (1) shortening of diastolic filling time of the ventricles and decrease in circulation to the ventricular muscle itself originated by tachycardia and (2) greater relative obstruction of the mitral orifice caused by an increased venous return to the heart.

MORPHINE TREATMENT OF ACUTE PULMONARY EDEMA

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The author believes that morphine or any similar alkaloid given by intravenous injection is very effective in the treatment of acute edema of the lungs. He has used it in fifty patients with acute edema of the lungs in doses of 1 or 2 centigrams. A favorable response was apparent in from two to five minutes after the injection; usually within approximately ten minutes the patient had practically recovered. No undesirable effects were noted. In some patients the extremities were bandaged. All patients received additional medication, but none were bled. The author points out that this method of therapy should be applied only in those patients who have crepitant râles and hemorrhagic sputum; he warns that if the pulmonary asphyxia and the dyspnea is of central nervous system origin, morphine must not be used.

HEART DISEASE AND PREGNANCY

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The rheumatic cardiovalvular disorders are almost the only ones to be considered here, since the age of the pregnant patient makes exceptional the occurrence of congenital as well as arterial or hypertensive heart disease.

There are three factors to be analyzed in connection with the tolerance of the pregnant woman to heart affections: (1) the mechanical factor inherent in the valvular lesion; (2) the factor of progressive development, inherent in the inflammatory process which causes the lesion; (3) the endocrine factor related to pregnancy. The factor of evolution is the most important of all three since the majority of pregnant heart patients requesting medical care have mitral stenosis (75 per cent in our statistics), which is the most progressive form of rheumatic lesion of the heart. It is, therefore, essential to understand clearly what decisions may have to be made in a pregnant patient with mitral stenosis. The prognosis depends upon the establishment of the diagnosis, and upon whether the rheumatic heart affection remains stationary or progresses. It should be recognized, however, that some patients with mitral disease present signs of activity of the rheumatic disease after delivery. It is important, therefore, to watch these patients before and after delivery and to eliminate, as far as possible, everything that may reactivate the rheumatic state.

All acute accidents occurring in patients with mitral stenosis are formal indications for interruption of pregnancy. These include the onset of auricular fibrillation, hemoptysis, acute edema of the lungs, and hemiparesis. It is necessary to remember that previous successful pregnancies do not guarantee the favorable outcome of a given pregnancy, because the involvement may have progressed since the previous pregnancy.

For the interruption of pregnancy, surgical methods rather than medical methods are advised; embolic accidents are thereby reduced. Whenever interruption of pregnancy is indicated in a patient with mitral stenosis, sterilization is clearly in order.

INTERMITTENT VENTRICULAR TACHYCARDIA IN YOUTH.
REPORT OF CASE WITH FATAL TERMINATION

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Instances where young people exhibited paroxysms of ventricular tachycardia, lasting a few seconds to a few minutes, separated by periods of normal rhythm or extrasystoles of the same type as those constituting the paroxysms, were described in 1927 by Gallavardin and Veil, as *tachycardic en salves*. Wilson and associates and Anderson reported on patients with similar conditions in 1931 and 1932. There were no signs of heart disease present, and the irregularity was generally considered to carry a good prognosis. Other cases have been reported, but the total number is not large.

That the prognosis under such circumstances is not necessarily always favorable is suggested by the following case report:

E. M., a male medical officer, 26 years of age, was found dead in his tent during the Borneo campaign of 1945. He had appeared to be perfectly well immediately before. No autopsy was performed.

This medical officer had presented himself to me in 1937, as an example of cardiac arrhythmia for presentation to his fellow medical students. He had played football strenuously throughout the whole of his school and undergraduate

career, without any undue distress, fatigue, or palpitation. Physical examination revealed a grossly irregular heart beat, no clinical cardiac enlargement, and no thrills or murmurs in any area. The arteries seemed normal. Blood pressure was 125/95. The chaotic heart action was uninfluenced by exercise, atropine, or carotid sinus stimulation. He was a nonsmoker. Standard limb lead electrocardiograms revealed a basic sinus arrhythmia (P-R interval 0.12 second), interrupted by (1) frequent right ventricular extrasystoles, often coupled, followed by pauses of variable length; (2) short salvos of ventricular tachycardia, slightly irregular in rhythm, commencing prematurely and followed by regular compensatory pauses. The number of complexes per paroxysm usually varied between six and nine. The sinus complexes were not remarkable, apart from a high voltage. Their form gave no indication of the presence of coronary disease. Unfortunately, no precordial leads were obtained.

X-ray study revealed a slight increase in transverse diameter corresponding to the "athletic heart." The past medical history was entirely uneventful. The irregularity had been noted at the age of 3 years and had been considered to be due to multiple extrasystoles and of no significance. There had been no complaints referable to the cardiovascular system during the remainder of his medical course or internship. He was at first rejected for naval or military service, but because of his fine physique and physical record, he was ultimately accepted and sent overseas.

The value of quinidine was suggested to him when the true nature of the irregularity was first recognized, but it was later discovered that he had never followed this advice. Whether quinidine plus avoidance of battle strain in the tropics would have lengthened his life is purely speculative. It is not proved but is less speculative to assume that his death was due to ventricular fibrillation or standstill.

This patient is reported on to redirect attention to a rare form of intermittent ventricular tachycardia which is unassociated with signs of organic heart disease, and which may be termed the "Gallavardin" type. This disturbance may begin in infancy and may occasionally terminate in sudden death in the absence of the protective effects of quinidine.

THE TREATMENT OF CONGESTIVE HEART FAILURE

MAHLON C. COOLEY, M.D., LOS ANGELES, CALIF.

Treatment of congestive heart failure has not changed much in ten years, but as we now better understand the disease and comprehend more fully methods of treatment, we apply treatment to the disease unhesitantly and with definite expectancy.

Rest is being studied as a definite remedy requiring a dosage to meet the particular need of an individual patient. No longer is there insistence upon a particular kind of rest (bed, chair, recumbent, and sitting). The criterion is rest of the heart muscle, thus saving the optimum number of heart beats consistent with the heart functioning as a good pump and a rhythmic one.

The sedative armamentarium is without recent change.

Morphine is still the drug of choice in the majority of cases. The contraindications are few but important. Due caution should be observed. In certain psychoneurotic complications, the exhibition of appropriate doses of phenobarbital, sodium bromide, or chloral hydrate is worthy of consideration.

Digitalis is yet the drug of choice, because it is the only drug which, by its triple action on nerve, conducting tissue, and muscle, reverses the state, slows the heart, regulates the rhythm and strengthens the contraction, and results in the

optimum: a better pump, a rhythmic pump, and a more rested one. Powdered leaf is evidently the most used preparation with certain pure glycosides gaining rapidly in favor. Tincture of digitalis for apparent good reason is being used less and less frequently. Cedilanid is the most potent of the glycosides but should be reserved for emergencies and for those patients in whom oral administration is impossible. Digitoxin is the preparation which merits the favor it is rapidly gaining. It has many advantages over digitalis leaf: injectability, stability, and accurate dosage. The prophesy that digitoxin will replace digitalis in a few years is not without supporting evidence.

The relation of salt restriction to the solution of the difficult problem of edema has claimed much attention in recent months. Without any doubt, thorough and proper handling of salt restriction, that is, restricting salt to a minimum through the aid of proper diet instruction, is a notable advance in cardiac therapeutics. Not only is there a lessening of ventricular strain, but the patient is rendered happier by being able to quench a normal thirst as well as prevent dehydration.

The following papers read before the Inter-American Congress of Cardiology, Mexico, D. F., Oct. 5-12, 1946, will be published in a later issue of the JOURNAL:

Weight of the Red Blood Corpuscles in Heart Failure Determined With Labelled Erythrocytes During and After Decompensation. G. Nylin, M.D., and S. Hedlund, M.D., Stockholm, Sweden.

Circulatory Adaptations in Ayerza's Syndrome—Black Cardiacs. Alberto C. Taquini, M.D., J. C. Fasciolo, M.D., J. R. E. Suarez, M.D., and H. Chiodi, M.D., Buenos Aires, Argentina.

The Diagnosis of Tricuspid Valve Disease. Salvador Aceves and Rafael Carral, Mexico, D. F., Mexico.

Comparative Study of the Intracavity Potential in Man and in Dog. Demetrio Sodi Pallares, M.D., Mario Vizcaino, M.D., Jorge Soberón, M.D., and Enrique Cabrera, M.D., Mexico, D. F., Mexico.

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*Executive Committee.

PROGRAM OF THE ANNUAL MEETING AND TWENTIETH SCIENTIFIC MEETING OF THE AMERICAN HEART ASSOCIATION, INC.

TO BE HELD AT THE HOTEL PRESIDENT, ATLANTIC CITY, N. J.,
JUNE 6 AND 7, 1947

ANNUAL MEETING

This important meeting, as well as a meeting of the representatives of local heart associations will be held in the Ballroom of the Hotel President beginning at 9:00 A.M., June 6, 1947.

ANNUAL DINNER

This will be held in the Ballroom of the Hotel President at 7:30 P.M., June 7, 1947. "Top Nazis" will be the subject of a talk by Colonel Ellis C. Vander Pyl. Colonel Vander Pyl, of Chief Operations Section, War Crimes Branch, United States Army, was for many months in close contact with top-ranking Nazis during war trials in Nürnberg. He will relate his associations with Goering, Hess, and the entire coterie who made world headlines. The toastmaster will be Dr. Howard F. West. Dress will be informal.

SCIENTIFIC MEETING*

The program for the three scientific sessions has been prepared by the following committee:

J. M. Askey, M.D., Los Angeles
 Emmet B. Bay, M.D., Chicago
 Herriman L. Blumgart, M. D., Boston
 George E. Burch, M.D., New Orleans
 Ignacio Chávez, M.D., Mexico City
 Douglas Deeds, M.D., Denver
 Arthur C. DeGraff, M.D., New York
 Norman E. Freeman, M.D., San Francisco
 Franklin Johnston, M.D., Ann Arbor
 John D. Keith, M.D., Toronto
 Robert L. King, M.D., Seattle

Chester M. Kurtz, M.D., Madison
 William B. Kountz, M.D., St. Louis
 E. Sterling Nichol, M.D., Miami
 Irvine H. Page, M.D., Cleveland
 William B. Porter, M.D., Richmond
 Ramon M. Suárez, M.D., Santurce, P. R.
 Helen B. Taussig, M.D., Baltimore
 J. Ross Veal, M.D., Washington, D. C.
 Merritt B. Whitten, M.D., Dallas
 Francis C. Wood, M.D., Philadelphia
 Edgar V. Allen, M.D., Rochester, Minn.
 (Chairman)

First Scientific Meeting, 2 P.M., June 6, Ballroom, Hotel President

Chairman, Howard F. West, M.D., President, American Heart Association; Secretary,
 Howard B. Sprague, M.D.

1. The Immediate Electrocardiographic Effects of Circumscribed Myocardial Injuries; An Experimental Study.
 Raymond D. Pruitt, M.D., Rochester, Minn., and Fernando Valencia, M.D., Ann Arbor, Mich.
 Discussion to be opened by Harold J. Stewart, M.D., New York. William Dressler, M.D., New York, and A. M. Master, M.D., New York.
2. The Varied Clinical Syndromes Produced by Dissecting Aneurysm.
 Samuel Baer, M.D., and Harold L. Goldburgh, M.D., Philadelphia.
 Discussion to be opened by William B. Kountz, M.D., St. Louis.
3. Physiologic Studies in Congenital Heart Disease.
 Richard J. Bing, Leroy D. Vandam, and Frank D. Gray, Jr., Baltimore.
 Discussion to be opened by Raymond S. Megibow, M. D., New York.
4. The Effect of Occlusive Arterial Diseases of the Extremities on the Blood Supply of Nerves.
 Joseph T. Roberts, M.D., Washington, D. C.
 Discussion to be opened by Norman E. Freeman, M.D., San Francisco, and Meyer Naide, M.D., Philadelphia.
5. Studies on the Collateral Circulation of Hearts With Acute Coronary Occlusion.
 Myron Prinzmetal, M.D., Los Angeles.
 Discussion to be opened by Herriman L. Blumgart, M.D., Boston.
6. Changes in the Coronary Arteries of Dogs Following Injections of Allylamine.
 L. L. Waters, M.D., New Haven.
 Discussion to be opened by Irving Greenfield, M.D., Woodmere, N. Y.
7. The Effect of Local Compression Upon Blood Flow in the Extremities of Man.
 Robert W. Wilkins, M.D., M. H. Halperin, M.D., and C. K. Friedland, M.D., Boston.
 Discussion to be opened by Geza de Takats, M.D., Chicago.

*Essayists, except the George Brown Memorial Lecturers, will be restricted to a maximum of fifteen minutes. Each must leave a completed manuscript with the secretary for consideration for publication in the AMERICAN HEART JOURNAL. Each prospective discussor will indicate his wishes in a notation including name, address, and presentation to be discussed which will be handed to the secretary. Each discussion will be from the rostrum and may not exceed three minutes. Questions lacking general interest should be directed to essayists privately after discussion has been completed.

Second Meeting, 9:00 A.M., June 7

Chairman, J. Ross Veal, M.D., Chairman Section on Peripheral Vascular Diseases;
Secretary, Grace Roth, Ph.D.

8. The Functional Pathology of Experimental Trench Foot.
Kurt Lange, M.D., David Weiner, M.D., and Linn J. Boyd, M.D., New York.
9. *The George Brown Memorial Lecture:*
A Consideration of Approximately Four Hundred Patients With Pulmonary Stenosis or
Atresia Who Were Treated by Surgical Means.
Helen B. Taussig, M.D., and Alfred Blalock, M.D., Baltimore.
10. Relief of Cardiac Pain by Local Block of Somatic Trigger Areas.
H. Seymour Rinzler, M.D., and Janet Travel, M.D., New York.
Discussion to be opened by David Davis, M.D., Boston, and Maurice S. Jacobs, M.D.,
Philadelphia.
11. Combined Heparin-Dicumarol Therapy of Myocardial Infarction.
Helen I. Glueck, M.D., Victor Strauss, M.D., and Johnson McGuire, M.D., Cincinnati.
Discussion to be opened by E. Sterling Nichol, M.D., Miami, Irving S. Wright, M.D.,
New York, and Nelson W. Barker, M.D., Rochester, Minn.
12. The Experience of Rheumatic Patients Who Served in the Armed Forces.
May G. Wilson and Joan W. Payson, New York.
Discussion to be opened by Leo M. Taran, M.D., New York, Benedict F. Massell, M.D.,
Boston, and George C. Griffith, M.D., Pasadena.
13. The Determination of the Prognosis of Pregnancy in Rheumatic Heart Disease.
Joseph J. Bunim, M.D., and Jeanette Rubricius, M.D., New York.
Discussion to be opened by John J. Sampson, M.D., San Francisco.

Third Meeting, 2:00 P.M., June 7

14. Newer Concept of Stokes-Adams Syndrome.
Sidney Schnur, M.D., Houston.
Discussion to be opened by Stanford Wessler, M.D., Boston.
15. Electrocardiographic Analysis of Cases of Right Axis Deviation.
Charles E. Kossman, M.D., New York.
Discussion to be opened by Harry Vesell, M.D., New York, Stephen R. Elek, M.D., Los
Angeles, and H. R. Miller, M.D., New York.
16. Studies in Fluorocardiography.
A. A. Luisada, M.D., F. G. Fleischner, M.D., and M. B. Rappaport, M.D., Boston.
Discussion to be opened by George F. Ellinger, M.D., Philadelphia, and Marcy L. Sussman,
New York.
17. The Present Status of Venography in Venous Thrombosis.
Hugh H. Hussey, M.D., and J. Ross Veal, M.D., Washington, D. C.
Discussion to be opened by Edward A. Edwards, M.D., Boston.
18. Night Cramps in Human Extremities.
Harold K. Moss, M.D., and Louis G. Herrmann, M.D., Cincinnati.
Discussion to be opened by Ferdinand R. Schemm, M.D., Great Falls, Mont., and Emil
M. Isberg, M.D., Miami Beach.

QUESTIONS AND ANSWERS PERIODS

The American Heart Association With the American Medical Association
(The place of these meetings will be announced.)

Monday, June 9

- 9:00-11:00 A.M. The Use of Anticoagulants in Cardiovascular Diseases.
N. W. Barker, M.D., Irving S. Wright, M.D., and E. Sterling Nichol, M.D.
- 2:00- 4:00 P.M. The Diagnosis of Congenital Cardiovascular Diseases.
Herrman L. Blumgart, M.D., Helen B. Taussig, M.D., and Eugene Eppinger, M.D.

Tuesday, June 10

- 9:00-11:00 A.M. The Peripheral Arterial Diseases.
Irving S. Wright, M.D., and N. W. Barker, M.D.
- 2:00- 4:00 P.M. The Use of Drugs in Heart Diseases.
Arthur C. DeGraff, M.D., Harry Gold, M.D., and Howard B. Sprague, M.D.

Wednesday, June 11

- 9:00-11:00 A.M. Hypertension.
I. H. Page, M.D., M. H. Barker, M.D., and J. Q. Griffith, M.D.
- 2:00- 4:00 P.M. Rheumatic Fever.
R. Duckett Jones, M.D., May G. Wilson, M.D., and George C. Griffith, M.D.

Thursday, June 12

- 9:00-11:00 A.M. Surgical Treatment for Vascular Diseases.
Norman E. Freeman, M.D., Geza de Takats, M.D., and J. Ross Veal, M.D.
- 2:00- 4:00 P.M. Problems in Electrocardiography.
Charles T. Wolferth, M.D., Franklin Johnston, M.D., and George Burch, M.D.

Friday, June 13

- 9:00-11:00 A.M. Management of the Failing Heart.
Francis C. Wood, M.D., Graham Asher, M.D., and James V. Warren, M.D.

THE American Heart Association was founded in 1924 "for the study of and the dissemination and application of knowledge concerning the causes, treatment and prevention of heart disease; the gathering of information on heart disease; the development and application of measures that would prevent heart disease; seeking and provision of occupations suitable for heart disease patients; the promotion of the establishment of special dispensary classes for heart disease patients; the extension of opportunities for adequate care of cardiac convalescents; the promotion of permanent institutional care for such cardiac patients as are hopelessly incapacitated from self-support; and the encouragement and establishment of local associations with similar objects throughout the United States."

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The American Council on Rheumatic Fever, organized in 1944, consists of a group of representatives of all national medical organizations concerned with rheumatic fever. It operates administratively through the American Heart Association and carries out the program of the American Heart Association insofar as that relates to rheumatic fever.

Annual membership in the American Heart Association is \$2.50 and includes twelve issues of *Modern Concepts of Cardiovascular Disease*; Journal membership is \$10.00 and includes a year's subscription to the AMERICAN HEART JOURNAL (January-December), twelve issues of *Modern Concepts of Cardiovascular Disease*, and annual membership in the Association. Contributing membership starts at \$25.00 per year; patron membership is \$50.00 and over per year. Membership blanks will be sent upon request.

The Association earnestly solicits your support and suggestions for its work. Donations will be gratefully received and promptly acknowledged.

American Heart Journal

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Original Communications

SIGNIFICANCE OF ABNORMALLY SMALL QRS DEFLECTIONS IN ONE OR MORE PRECORDIAL LEADS

ALBERT W. LAPIN, M.D.*
MONTREAL, QUEBEC

LOW voltage of the QRS deflections in the standard limb leads has engaged the attention of many investigators since the early days of electrocardiography, and the significance attributed to it has undergone many fluctuations. In recent years, since the use of precordial leads has become more widespread, various reports have appeared on low voltage occurring in these leads. Several attempts have been made to show some correlation linking low voltage in the two types of leads, but there has been little agreement among different writers as to whether any correlation of this kind exists. There is, furthermore, no consensus as to whether low voltage in the precordial leads is of any important significance. The present study was undertaken partly to ascertain whether low voltage in the precordial leads has, as a rule, the same or a different origin than low voltage in the limb leads and whether it should be regarded as more, or less, important.

Before proceeding to a consideration of our findings it may be profitable to review some of the earlier work on the significance of low voltage occurring in the limb leads, in the precordial leads, or in both.

EARLIER OBSERVATION ON LOW VOLTAGE

Low Voltage in the Standard Limb Leads.—Low voltage is commonly considered to be present in the standard limb leads if the greatest deflection of the

From the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Mich.

Much of the work upon which this article is based was done with the aid of grants to Dr. Frank N. Wilson from the Horace H. Rackham School of Graduate Studies and the S. S. Kresge Foundation.

*Clinical Fellow in Medicine of the American College of Physicians for the year 1946. Demonstrator in Medicine, McGill University.

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QRS complex extends less than 5 mm. above or below the base line in all of them, when the electrocardiograph is so standardized that the introduction of 1 mv. into the circuit produces a deflection of 10 millimeters.

In 1926 three papers dealing with low voltage appeared in the American literature, and all three took a gloomy view of its significance. Sprague and White,¹ reviewing fifty-seven cases, concluded: "Excluding the temporary effect of hypothyroidism, low voltage has never been found in our experience in records from normal hearts." Hepburn and Jamieson² summed up their experience thus: "Low voltage (even when) unaccompanied by other electrocardiographic abnormalities is a prognostic sign of serious import." On statistical grounds they considered it to rank second only to bundle branch block as an electrocardiographic sign of ill omen. Master and Pardee³ included low voltage among a number of specified graphic abnormalities that are "indicative of a diseased heart."

In the following year there appeared a paper by Willius and Killins,⁴ whose conclusions were almost directly opposite to those of the previous investigators. They reported a series of 140 electrocardiograms showing low voltage as the sole deviation from the normal, and they concluded that low voltage not accompanied by other graphic abnormalities does not necessarily imply that serious myocardial damage is present. Later studies, likewise carried out on hospital patients, gave intermediate results. Turner,⁵ in 1932, reported low voltage in the standard limb leads in about 3 per cent of the routine electrocardiograms taken at the Presbyterian Hospital in New York. He analysed 164 cases and found that 113 of the patients had manifest heart disease and sixty-three of these were in congestive failure; of the remaining fifty-one patients with no organic cardiac disease, twelve had edema or fluid collections in the serous sacs. Barrit,⁶ in a hospital series of ninety-four patients, found that when low voltage was accompanied by abnormal T waves there was a much higher incidence of heart disease than when it was the sole graphic abnormality but that even in the latter case heart disease was present in 45 per cent of the patients.

One obvious reason for such divergent conclusions is that the different observers were studying records taken on selected cases and not on "random samples." Before the significance of low voltage could be critically appraised, it was necessary to know its incidence as a physiologic variant in the records of normal persons, and up to the time of the early studies mentioned, no large series of such records had been published. During the past ten years, however, a considerable number of electrocardiograms of healthy persons have been collected and studied by various authors: Table I gives in summary the incidence of low voltage in the standard limb leads in seven such series, totalling 5,500 normal persons. One study was made on a group of college students,¹⁴ two on groups of military aviators,^{2,11} others on business and professional men whose ages ranged from 30 to 60 years,^{5,12} and one series included women,¹³ so that both sexes and a wide range of ages were represented.

Of the total of 5,500 persons, only sixty, or 1.09 per cent, showed low voltage in the standard limb leads. The incidence in each of the separate series is in quite good agreement with this figure, ranging from 0 to 1.6 per cent.

TABLE I. INCIDENCE OF LOW VOLTAGE IN STANDARD LIMB LEADS OF 5,500 HEALTHY INDIVIDUALS

SERIES	TOTAL NUMBER	NUMBER WITH LOW VOLTAGE	PER CENT
Crawford ⁷	1,000	14	1.4
Johnson ⁸	2,400	26	1.09
Graybiel and co-workers ⁹	1,000	16	1.6
Stewart and Manning ¹¹	500	1	0.2
Larsen and Skulason ¹²	100	0	0
Shipley and Halloran ¹³	200	3	1.5
Bellet and Kershbaum ¹⁴	300	0	0
Total	5,500	60	1.09

It is apparent from these data that while low voltage in the limb leads may occur in the electrocardiograms of healthy persons, it is an uncommon finding, occurring not much oftener than once in one hundred observations.

One other series is mentioned separately, because its figures are quite different from the rest. This is the report of a study made on 173 civil airline pilots¹⁰ in whose standard limb leads low voltage was found in fourteen, or 8 per cent of the subjects. These pilots were in the same age group as many of the persons in the other series reported in the foregoing discussion, and it is difficult to account for the much higher incidence of low voltage. If these figures are added to the totals in Table I, then of a total of 5,673 healthy persons, there are seventy-four with low voltage, an incidence of 1.3 per cent.

Low Voltage in the Precordial Leads.—With regard to low voltage in the precordial leads, the literature contains a number of reports,¹²⁻¹⁶ but for various reasons it is not easy to compare one with another. The method of selecting cases varied from one series to another, and the several investigators did not use the same locations for either exploring or indifferent electrodes. It will probably suffice for our purpose to consider in detail only two of the papers that were published up to 1941.^{14,16} Both of these deal specifically with the pathologic significance of low voltage in the precordial leads and both contain comprehensive reviews of earlier work on the subject.

Leach, Reed, and White¹⁶ studied the relationship between the amplitudes of the deflections in the standard limb leads and their size in a single unspecified precordial lead from the region of the apex impulse (probably CF₄). They considered low voltage to be present in this lead when the voltage of the largest QRS deflections in either direction did not exceed 0.5 millivolts. They collected 100 cases with low voltage in the standard leads and normal voltage in Lead IV (Group 1); 100 cases with low voltage in Lead IV and normal voltage in the standard leads (Group 2) and 100 cases with low voltage in both (Group 3). They found evidence of heart disease in 57 per cent of the total composite series of 300 cases: in 65 per cent of Group 1 and in 63 per cent of Group 3 but only in 47 per cent of Group 2 (low voltage in the precordial lead alone). They con-

cluded that not only heart disease, but also general debilitating diseases, changes in the position of the heart, and changes in the conductivity of the adjacent tissues are factors in the production of low voltage; and that, in addition, the thickness of the chest wall and the position of the precordial electrode (they were using only one precordial lead) influenced the voltage of QRS in Lead IV. It was their opinion that the finding of low voltage QRS deflections, whether in the limb or the precordial leads, is, by itself, of little diagnostic value. Since 10 per cent of their entire series of 300 individuals were perfectly healthy, it did not appear to furnish a valuable clue as to the presence or absence of cardiac or noncardiac disease.

Bellet and Kershbaum,¹⁴ studying the same problem, arrived at a rather different conclusion. They collected twenty cases showing low voltage in both limb and precordial leads. In each of these, three precordial leads had been taken, and they required that all show small deflections before low voltage was considered to be present. Most of these cases had been studied before the American Heart Association and the Cardiac Society of Great Britain and Ireland had announced the joint recommendations of their Committees on Standardization of Precordial Leads,¹⁷ and the chest leads used were not, for the most part, those later recommended. They consisted of one from apex to left leg, one from apex to back, and one from left scapula to left leg, so that only one of the precordial positions specified by the Committees on Standardization was included, namely, the region of the apex impulse. In all twenty patients there was evidence of severe myocardial damage, and in eleven myocardial infarction was present. In a control group of fifty patients with low voltage in the limb leads, but normal voltage in the precordial leads, the incidence of severe myocardial damage was much less. It was concluded that whereas the limb leads might show low voltage as a result of extracardiac factors such as edema, serous effusion, emphysema, or an unusual position of the heart in the thorax, the precordial leads are not, as a rule, affected by such factors, and low voltage in these leads is due in almost all cases to serious myocardial disease.

MATERIAL AND METHODS EMPLOYED IN THE PRESENT STUDY

Our material consisted of 100 electrocardiograms showing low voltage in the standard limb leads, drawn in chronological order from the files of the Heart Station and each accompanied by a full set of six precordial leads. These 100 cases were then separated into two main groups, depending on whether or not low voltage occurred in any of the precordial leads as well. The precordial leads were taken from the chest positions C_1 to C_6 specified by the Committees on Standardization,¹⁷ with Wilson's central terminal¹⁸ as the indifferent electrode.

In a series of this type, collected in a hospital, an element of special selection is inevitably introduced, because it is the practice in most clinics to order electrocardiograms only on patients who are strongly suspected of having heart disease; moreover, patients with certain types of cardiac disease are more likely to have precordial leads ordered than are others. The resulting series can therefore hardly be considered a random sample of the general population, or even

of the hospital population. This defect in sampling is freely acknowledged, but it need not be given too much weight in the case of the present study, since we do not intend to draw any broad conclusions as to the numerical incidence of specific diseases associated with low voltage but rather to ascertain what physiologic changes are common to the various types of case in which low voltage occurs.

Criteria for Low Voltage.—In the standard limb leads the specifications of the Criteria Committee of the New York Heart Association³¹ were adopted, low voltage being considered to be present when the greatest deflection of the QRS complex does not extend more than 5 mm. above or below the base line in any of the three leads.

It was more difficult to arrive at a satisfactory definition of low voltage in the precordial leads. Others have applied to these leads the same criteria as in the case of the standard limb leads, but it seemed to us that this was hardly justifiable since the mean size of the deflections in the precordial leads is normally so much greater. It was necessary as a preliminary step to consider the range in amplitude of the ventricular deflections in the precordial electrocardiograms of healthy individuals whose curves had been taken with the same technique as that used in our cases. In this way a standard minimal voltage could be set for each lead, and any considerably smaller voltage could reasonably be designated as low. Two studies satisfactory for our purpose have been reported.

Kossmann and Johnston,¹⁸ using Wilson's central terminal and the chest positions C₁ to C₅, studied the precordial Leads V₁, V₂, V₃, V₄, and V₅ in thirty normal students. Table II represents a condensation of some of their findings: it lists the minimum, maximum, and mean values for the amplitude of the R, S, and RS deflections in each lead. The RS, or intrinsic deflection in any lead, is measured by adding the voltages of the R and S deflections; this gives a truer representation of the magnitude of the potential variations than does the largest QRS deflection measured from the base line. The minimum values found for the RS deflection were 1.5 mv in Lead V₂, 1.26 mv in Lead V₃, 1.8 mv in Lead V₄, and 1.12 mv in Lead V₅.

TABLE II. MEASUREMENTS OF THE QRS DEFLECTIONS IN THE PRECORDIAL LEADS, EXPRESSED IN TENTHS OF A MILLIVOLT*

LEAD	R			S			RS		
	MIN.	MAX.	MEAN	MIN.	MAX.	MEAN	MIN.	MAX.	MEAN
V ₁	1.0	9.6	4.16	3.4	24.0	11.05	6.6	26.8	15.21
V ₂	4.0	20.8	9.05	3.0	38.8	16.23	15.0	46.0	25.27
V ₃	6.0	54.6	16.70	0.0	22.0	9.05	12.6	54.6	25.75
V ₄	12.2	46.0	22.31	0.0	16.0	5.32	18.0	51.6	27.63
V ₅	8.8	33.0	18.78	0.0	9.6	1.93	11.2	33.2	20.70

*Adapted from Kossmann and Johnston.¹⁸

Bryant,²⁰ using the same technique, measured the RS deflection in Leads V_2 and V_4 in the electrocardiograms of 103 normal persons. In each of these leads the minimum voltage was 1.0 millivolts.

If the findings in these two series are combined, then the minimum values for the RS deflection in each lead are: 1.0 mv in Lead V_2 , 1.26 mv in Lead V_3 , 1.0 mv in Lead V_4 , and 1.12 mv in Lead V_5 .

Neither Kossmann and Johnston nor Bryant included Lead V_6 in their studies. This is a lead from the left midaxillary line at the level of the apex impulse. It has perhaps a closer relationship to the standard limb leads than have most of the other precordial leads, since it is influenced chiefly by electrical forces more nearly in the frontal plane. In order to ascertain the range of its amplitude in normal individuals as well as to add to the number of cases in which the other precordial leads had been studied, we measured the intrinsic deflections of Leads V_2 , V_3 , V_4 , V_5 , and V_6 in 100 cases with normal amplitude in the limb leads. These were not necessarily all normal records, but we did exclude cases of anterior, lateral, and posterolateral infarction, since these are commonly the cause of small QRS deflections in Leads V_4 , V_5 , and V_6 . In these 100 cases, an RS deflection of 0.9 mv or less occurred only once in Lead V_2 , twice in Lead V_3 , once in Lead V_4 , and in no case in Lead V_5 , and an RS of 0.7 mv or less occurred only twice in Lead V_6 . Accordingly it appeared reasonable to accept as arbitrary values for low voltage a total RS deflection of 0.9 mv or less in Leads V_2 , V_3 , V_4 , V_5 and of 0.7 mv or less in Lead V_6 . These figures are all well below the minimum values found by Kossniann and Johnston and by Bryant.

Low voltage in Lead V_1 was not considered to have any significance for our purpose, since there is quite a wide variation in the amplitude of its deflections in normal persons.

RESULTS

Using the criteria specified, we found that of the main group of 100 patients showing low voltage in the standard limb leads (to which we shall for convenience hereafter refer as Group A), sixty-five (to be designated subgroup B) showed low voltage in one or more of the precordial leads as well. Table III shows the distribution by diagnosis of the patients in both main group and subgroup. In both, the commonest diagnosis was myocardial infarction, which was present in forty-three of the 100 in the main group and thirty-five of the sixty-five in the subgroup. Of the remaining fifty-seven patients in the main group, thirty-seven had extracellular collections of fluid (hydrothorax, hydropericardium, ascites, marked congestion or edema of the lungs, or subcutaneous edema) and two had pronounced pulmonary emphysema. In the subgroup there were thirty patients without myocardial infarction and of these, nineteen had extracellular collections of fluid (twelve had hydrothorax, six had marked congestion or edema of the lungs, one had subcutaneous edema only) and one had pulmonary emphysema.

In the main group there were six patients and in the subgroup four patients with no evidence of heart disease and without extracellular fluid accumulations, obesity, emphysema, or hypothyroidism.

TABLE III. GROUP A, 100 PATIENTS IN WHOM LOW VOLTAGE OCCURRED IN STANDARD LIMB LEADS; SUBGROUP B, 65 OF PATIENTS IN GROUP A IN WHOM LOW VOLTAGE OCCURRED IN PRECORDIAL LEADS ALSO

	GROUP A			SUBGROUP B		
Myocardial infarction						
With extracellular fluid						
Hydrothorax, etc.	7			7		
Pulmonary congestion or edema	11			7		
Peripheral edema only	2			0		
Total with extracellular fluid		20			14	
Without extracellular fluid		23			21	
Total myocardial infarcts			43			35
Arteriosclerotic heart disease						
With extracellular fluid						
Hydrothorax, etc.	7			4		
Pulmonary congestion or edema	10			6		
Peripheral edema only	9			1		
Total with extracellular fluid		26			11	
Without extracellular fluid		8			4	
Total arteriosclerotic heart disease			34			15
Constrictive pericarditis, with hydrothorax			4			3
Hodgkin's disease, with hydrothorax			1			1
Carcinoma of liver, with ascites			1			0
Foreign body in heart, with hydrothorax			1			1
Metastatic carcinoma of heart, with hydrothorax			1			1
Massive pulmonary embolus with gangrenous infarct			1			0
Rheumatic heart disease, with hydrothorax			3			2
Rheumatic heart disease, peripheral edema only			1			0
Idiopathic cardiac hypertrophy			2			2
Pulmonary emphysema, severe			2			1
No heart disease (no emphysema, serous effusion, edema, obesity, or myxedema)			6			4
Total			100			65

Table IV lists in detail the sixty-five cases included in subgroup B, all showing low voltage in one or more of the precordial leads as well as in the standard limb leads. It gives the age, sex, diagnosis, height of the P and T waves, presence or absence of serous effusion, congestion of the lungs, and peripheral edema; and it gives the amplitude of the RS deflection in each of Leads V₄, V₅, and V₆, as well as in the lead in which it is greatest.

It will be noted that in only three instances were the deflections low in all six precordial leads. One of these patients had a hydropneumopericardium; one had cardiac hypertrophy of undetermined etiology, without congestive failure; the third was a young woman, 31 years of age, without evidence of any organic disease.

Low voltage occurred in three precordial leads in twelve cases; in two leads in twenty-six cases; and in a single lead in twenty-four cases.

It occurred in Lead V₂ in three cases, in Lead V₃ in four cases, in Lead V₄ in twenty-two cases, in Lead V₅ in forty cases, and in Lead V₆ in fifty-six cases.

TABLE IV. MEASUREMENTS OF RS, P, AND T DEFLECTIONS IN TESTS OF A MILLIVOLT

CASE	SEX	AGE	RS V ₁	RS V ₂	RS V ₃	LARGEST RS DEFLECTION	P	T	CLINICAL DIAGNOSIS	PLEURAL OR PERICARDIAL EFFUSION OR ASCITES	CONGESTION OR EDEMA OF THE LUNGS	PERIPHERAL EDEMA	OTHER CLINICAL FEATURES
1	M	38	10	6	7	V ₂ 25	1.5	4.0	Myocardial infarction	0	0	0	Bilateral hydrothorax
2	M	54	9	4	4	V ₃ 14	0.75	3.0	Myocardial infarction	0	0	0	Ascites
3	F	41	6	1	4	V ₂ 22	2.0	2.5	Myocardial infarction	0	0	0	Left hydropneumothorax
4	M	49	14	14	7	V ₃ 14	1.0	2.5	Myocardial infarction	0	0	0	Hydrothorax and ascites
5	M	57	17	7	5	V ₃ 30	1.0	0.5	Myocardial infarction	0	0	0	Bilateral hydrothorax
6	F	55	7	4	5	V ₂ 17	2.0	1.0	Myocardial infarction	0	0	0	Bilateral hydrothorax
7	M	45	23	14	2	V ₄ 23	1.5	0.0	Myocardial infarction	0	0	0	Hydrothorax and ascites
8	M	46	8	8	7	V ₂ 18	1.5	0.5	Myocardial infarction	0	0	0	
9	M	53	13	7	9	V ₂ 17	1.0	2.0	Myocardial infarction	0	0	0	
10	M	40	20	18	7	V ₃ 20	1.0	0.75	Myocardial infarction	0	0	0	
11	M	45	26	11	5	V ₄ 26	1.0	0.2	Myocardial infarction	0	0	0	
12	M	48	10	5	5	V ₂ 20	0.5	0.75	Myocardial infarction	0	0	0	
13	M	58	15	12	4	V ₃ 20	1.5	2.0	Myocardial infarction	0	0	0	
14	M	46	10	7	6	V ₂ 30	1.5	1.0	Myocardial infarction	0	0	0	
15	M	57	15	14	4	V ₂ 17	1.5	0.75	Myocardial infarction	0	0	0	
16	M	42	22	10	5	V ₄ 22	1.5	2.0	Myocardial infarction	0	0	0	
17	M	52	8	6	6	V ₂ 16	1.5	1.5	Myocardial infarction	0	0	0	
18	M	61	16	12	6	V ₄ 15	0.25	0.25	Myocardial infarction	0	0	0	
19	F	78	15	13	6	V ₄ 15	0.25	0.25	Myocardial infarction	0	0	0	
20	M	63	9	3	5	V ₃ 15	2.5	0.5	Myocardial infarction	0	0	0	
21	M	37	14	5	4	V ₂ 20	2.0	1.0	Myocardial infarction	0	0	0	
22	M	68	10	9	5	V ₂ 13	1.0	1.0	Myocardial infarction	0	0	0	
23	M	29	16	13	4	V ₂ 40	0.5	0.75	Myocardial infarction	0	0	0	
24	M	64	11	7	5	V ₁ 25	0.1	0.1	Myocardial infarction	0	0	0	
25	M	46	20	5	5	V ₂ 23	1.5	0.1	Myocardial infarction	0	0	0	
26	M	65	8	8	8	V ₃ 25	1.0	0.1	Myocardial infarction	0	0	0	
27	M	58	15	5	8	V ₂ 25	1.5	1.0	Myocardial infarction	0	0	0	

28	M	58	20	2	3	V ₃	22	0.1	0.1	Myocardial infarction	—	—	—	Hydrothorax
29	M	51	4	4	3	V ₂	11	1.5	1.5	Myocardial infarction	0	—	—	Emphysema
30	F	53	11	8	4	V ₂	14	1.0	0.5	Myocardial infarction	0	—	—	Pulmonary edema
31	M	51	7	3	4	V ₃	10	1.2	0.1	Myocardial infarction	0	—	—	Pulmonary edema
32	M	55	10	3	6	V ₂	30	1.5	1.0	Myocardial infarction	0	—	—	
33	M	56	18	6	5	V ₂	20	0.75	0.5	Myocardial infarction	0	—	—	Pulmonary infarct and pulmonary edema
34	M	63	9	3	5	V ₃	15	2.5	0.5	Myocardial infarction	0	—	0	
35	M	66	3	14	10	V ₄	17	1.5	1.75	Myocardial infarction	0	—	—	Pulmonary infarct with gangrene
36	F	60	6	7	6	V ₂	12	0.0	0.25	Arteriosclerotic heart disease	0	0	0	Obesity
37	F	47	9	12	10	V ₃	12	0.5	1.75	Hypertensive heart disease	0	0	0	
38	M	49	15	8	4	V ₄	15	1.2	1.2	Arteriosclerotic heart disease	0	0	0	Emphysema and obesity
39	M	68	15	12	5	V ₄	15	1.0	2.0	Arteriosclerotic heart disease	0	0	0	Carcinoma of sigmoid
40	M	53	15	7	4	V ₃	21	0.5	0.5	Arteriosclerotic heart disease	—	—	—	Bilateral hydrothorax
41	M	71	25	20	5	V ₄	25	0.25	0.25	Arteriosclerotic heart disease	—	—	—	Hypertension and bilateral hydrothorax
42	M	49	15	7	5	V ₃	21	0.0	0.1	Arteriosclerotic heart disease	0	—	—	Hypertension
43	M	48	7	8	8	V ₂	18	0.75	0.5	Arteriosclerotic heart disease	0	—	—	Hypertension
44	M	67	6	10	7	V ₃	10	0.5	1.0	Arteriosclerotic heart disease	0	—	0	Carcinoma of esophagus; infarct right lung
45	M	44	19	5	4	V ₃	21	1.5	0.5	Arteriosclerotic heart disease	0	—	—	Auricular fibrillation
46	M	58	18	12	6	V ₂	25	0.0	0.1	Arteriosclerotic heart disease	0	—	—	Emphysema
47	M	55	15	13	3	V ₃	15	1.5	0.75	Arteriosclerotic heart disease	—	—	—	Hydrothorax, auricular fibrillation
48	M	63	14	5	7	V ₃	28	0.0	0.1	Arteriosclerotic heart disease	—	—	—	Hypertension
49	M	54	13	12	7	V ₃	25	0.75	0.1	Arteriosclerotic heart disease	0	—	—	Bilateral hydrothorax; carcinoma of prostate
50	M	76	19	11	4	V ₄	19	1.0	1.25	Arteriosclerotic heart disease	—	—	—	

TABLE IV. MEASUREMENTS OF RS, P, AND T DEFLECTIONS IN TENTHS OF A MILLIVOLT—CONT'D

CASE	SEX	AGE	RS V ₁	RS V ₂	LARGEST RS DEFLECTION	P	T	CLINICAL DIAGNOSIS	PLEURAL OR PERICARDIAL EFFUSION OR ASCITES	CONGESTION OR EDEMA OF THE LUNGS	PERIPHERAL EDEMA	OTHER CLINICAL FEATURES
51	F	22	5	4	V ₂ 8	2.0	0.5	Tuberculous pericarditis	—	0	0	Pneumohydropericardium and pneumohydrothorax
52	M	52	7	4	V ₂ 10	1.5	0.1	Constrictive pericarditis	—	—	—	Bilateral hydrothorax and ascites
53	M	52	7	4	V ₂ 15	0.1	0.1	Constrictive pericarditis	—	—	—	Hydrothorax and ascites
54	M	54	6	5	V ₁ 18	0.5	0.5	Hodgkin's disease (mediastinal)	—	0	0	Massive left hydrothorax
55	M	56	9		V ₂ 17	0.6	0.5	Foreign body in ventricular wall	—	0	0	Hydrothorax and hydropericardium
56	M	41	9	7	V ₂ 23	1.5	0.1	Rheumatic heart disease; mitral stenosis	—	—	—	Bilateral hydrothorax
57	M	59	22	7	V ₄ 22	0.0	0.1	Rheumatic heart disease; mitral stenosis	—	—	—	Hydrothorax, right; auricular fibrillation
58	M	64	13	4	V ₄ 13	1.2	1.0	Metastatic carcinoma to heart and pericardium	—	—	0	Hydrothorax, right; carcinoma of trachea
59	F	36	11	4	V ₄ 11	1.75	0.10	Idiopathic hypertrophy	0	0	0	Bronchial asthma
60	F	20	4	5	V ₂ 8	1.5	0.75	Idiopathic hypertrophy	0	0	0	Psychoneurosis, neurocirculatory asthenia
61	M	47	11	4	V ₄ 12	1.5	2.5	Pulmonary emphysema	0	0	0	Carcinoma of stomach
62	F	31	9	4	V ₁ 9	1.0	1.0	No heart disease	0	0	0	Parosymal tachycardia
63	M	55	6	9	V ₂ 17	0.7	0.5	No heart disease	0	0	0	
64	F	53	9	4	V ₂ 12	1.75	1.0	No heart disease	0	0	0	
65	M	30	15	2	V ₂ 17	0.75	0.75	No heart disease	0	0	0	

In many instances the deflections were very large in some leads although small in one or more of the others. In twenty-nine of the sixty-five cases the largest RS deflection was 2.0 mv or more, and in one case it was 4.0 millivolts. The largest deflection occurred in Lead V_2 in twenty-seven cases, in Lead V_3 in eighteen cases, in Lead V_4 in fourteen cases, in Lead V_1 in three cases, and in Lead V_5 in three cases. This is in contrast to the usual finding in normal persons, where the mean amplitude of RS tends to increase from Lead V_1 to V_4 . This shift of the largest deflection toward the right (from Lead V_4 to V_2) suggests that the electrical axis was rotated from its normal position toward the sagittal plane.

PHYSIOLOGIC CONSIDERATIONS

Wilson pointed out in 1930, in a discussion of the factors theoretically capable of leading to a reduction in the amplitude of the electrocardiographic deflections, that such reduction might be accomplished in one or more of three ways:

1. By conditions that affect the efficiency of the myocardium itself, preventing it from developing an electromotive force of normal magnitude.
2. By conditions that alter the electrical conductivity of the tissues surrounding the heart.
3. By conditions that alter the direction of the mean electrical axis of the heart, thereby changing the size of its projection upon any given lead.

These three principles will be developed more fully later in this paper, when the various types of conditions that were found to be associated with low voltage in this series are discussed.

Conditions Affecting the Total Electromotive Forces Developed by the Myocardium.—Under this heading we shall discuss in particular myocardial infarction and arteriosclerotic heart disease. Myocardial infarction was the most common cardiac abnormality in both groups shown in Table III; it was present in forty-three of one hundred cases in Group A and in thirty-five of the sixty-five cases in subgroup B. To understand how this condition may give rise to low voltage it is instructive to compare a normal precordial electrocardiogram with those from typical cases of myocardial infarction.

The precordial leads of a healthy young man of 30 years are shown in Fig. 1,A. An R wave is present in all leads; it is relatively small in Lead V_1 and grows progressively larger in the leads from points farther to the left until it attains its maximum voltage of 2.1 mv in Lead V_4 ; it then becomes smaller again in Lead V_5 , and in Lead V_6 it is only 1.2 millivolts. The S wave is relatively large in Leads V_1 , V_2 , and V_3 , then rapidly diminishes until in Lead V_6 it is merely vestigial.

Fig. 1,B, represents the precordial electrocardiogram of a 46-year-old physician who had had an acute coronary occlusion five days before it was taken. It is entirely typical of anteroseptal myocardial infarction. In contrast to the normal record, A, the R wave is completely absent in Leads V_1 , V_2 , and V_3 and is only rudimentary in Lead V_4 . In each of these leads there is now only a deep

QS wave, reflecting the negative potential of the ventricular cavity which is transmitted passively through the electrically inert infarcted muscle. The fifth and sixth precordial positions were apparently somewhat lateral to the infarct and the still-healthy myocardium beneath them produced a positive potential as shown by the emergence of the R waves in Leads V_5 and V_6 , but the infarcted area was close enough to transmit some cavity negativity to the exploring electrode; moreover, the positivity previously contributed by the adjacent now-infarcted muscle has been withdrawn, with the result that these R waves did not attain their usual size. The RS-T elevation and late inversion of the T waves complete the electrocardiographic picture of recent infarction. The standard limb leads and unipolar extremity leads are shown in Fig. 1, C. They exhibit unusually small deflections but show no diagnostic features.

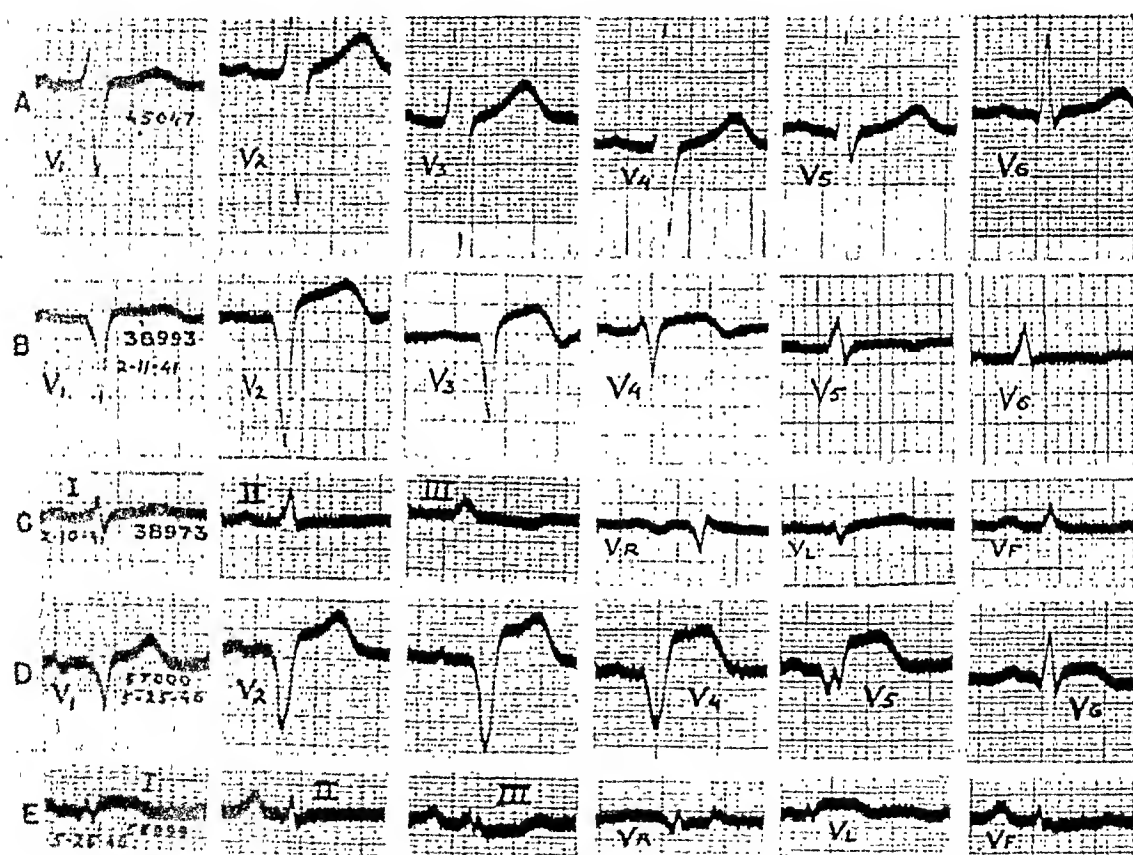


Fig. 1.—A. Normal precordial electrocardiogram. B. Precordial electrocardiogram of patient with recent anterior myocardial infarction, showing low voltage in Leads V_1 and V_2 . C. Low voltage in limb leads, same patient as in B. D and E. Electrocardiogram of another patient with anterior infarction, showing low voltage in Leads V_1 and V_2 and in the limb leads.

Fig. 1, D, represents the precordial electrocardiogram in another typical case of anterior myocardial infarction. The patient, a 63-year-old man, had had a coronary occlusion ten days before this record was taken. The precordial leads are very similar to those in the previous case, showing absence of the R waves and deep QS waves in Leads V_1 , V_2 , V_3 , and V_4 . In Lead V_5 the Q wave

is still present but is not very deep, and a small upward deflection that barely reaches the base line represents the R wave produced by surviving muscle under the exploring electrode. Lead V_6 shows a tiny Q wave also, but this lead was far enough lateral to the main area of infarction to have an R wave 7 mm. tall. The standard limb leads are shown in Fig. 1, *E*. In these the QRS complexes are small in all leads, reflecting the low amplitudes of Leads V_5 and V_6 ; there is a small Q wave in Lead I with upward displacement of RS-T and terminal inversion of the T wave. There is S-T depression in Lead III. The deflections in the unipolar extremity Leads V_R , V_L , and V_F are very small.

In both cases it will be seen that while the deflections in Leads V_5 and V_6 and in the limb leads are small, the deflections in Leads V_2 and V_3 are well within the normal range of amplitude. Because these leads from the right and mid-precordium are influenced chiefly by forces acting in the sagittal plane, they have little relationship to the limb leads. The latter lie in the frontal plane and are accordingly more likely to resemble Leads V_5 and V_6 .

Fig. 2 is particularly instructive as an example of conditions that may lead to a definite increase in QRS amplitude in certain precordial leads while at the same time producing a decrease in others and in the limb leads. It shows serial

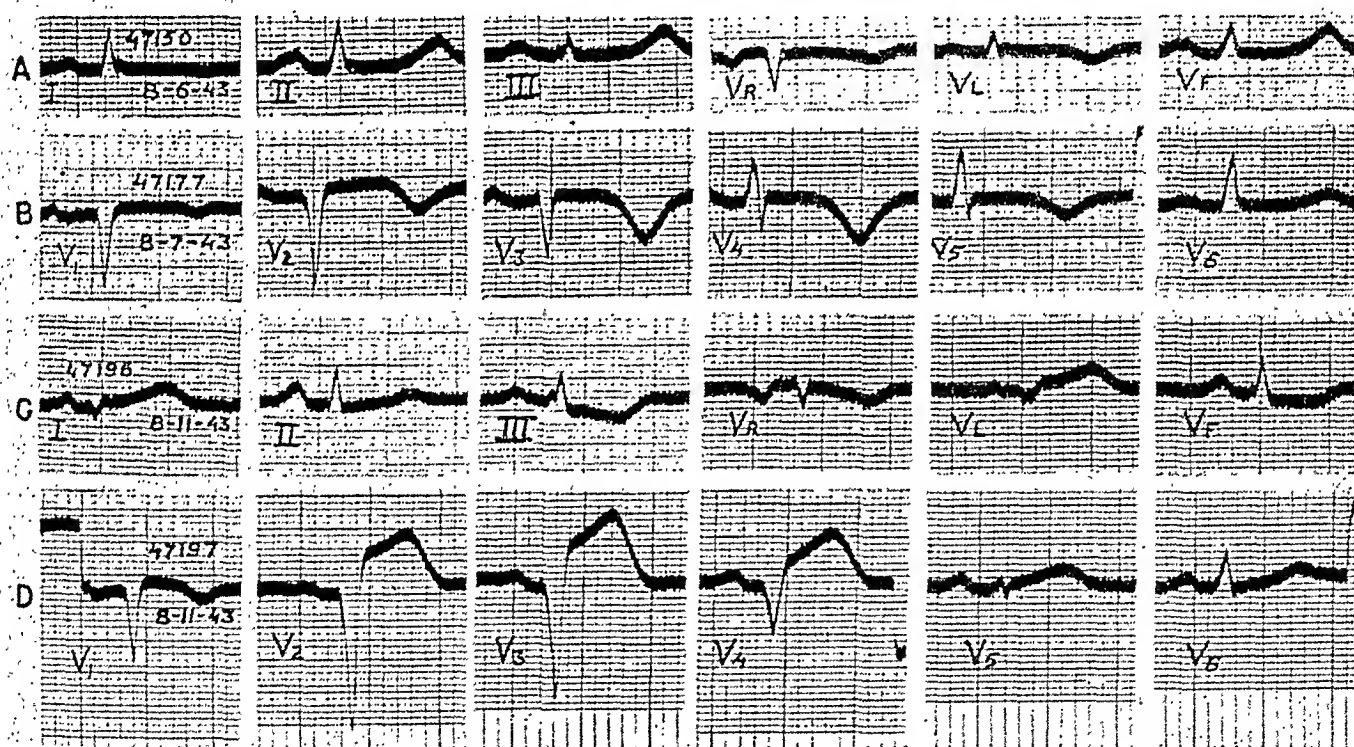


Fig. 2.—A and B, Electrocardiogram taken within twenty-four hours after the patient had had a small anterior infarct. C and D, Electrocardiogram of same patient four days later. With extension of the infarcted area, there has been an increase in the size of the deflections in Leads V_2 and V_3 but a decrease in Leads V_5 and V_6 and in the limb leads.

curves of a 41-year-old woman who had been known to have hypertensive and arteriosclerotic heart disease for some time. On Aug. 6, 1943, she had a sudden attack of severe persistent substernal pain. The standard limb leads shown in Fig. 2, *A*, were taken a few hours later and the precordial leads, *B*, the next day. The precordial leads indicate a small anteroseptal infarct; they show complete

absence of the R wave in Lead V_2 , an embryonic R wave in Lead V_3 , and deep inversion of the T waves in Leads V_2 , V_3 , V_4 , and V_5 . The patient continued to have pain, and it is most interesting to compare the first set of records described with those taken four days later, Aug. 11, 1943. In the case of the latter, Lead I.C, shows a Q wave not previously present and reduced QRS amplitude. The precordial leads, D, show changes suggesting that there has been a lateral extension of the infarct. The R wave, previously absent in Lead V_2 only, is now absent in Leads V_1 , V_2 , V_3 , and V_4 . The amplitude of the QS wave in V_2 and V_3 is much greater than it was on August 7, whereas in Leads V_5 and V_6 and in the limb leads the QRS amplitude has become distinctly smaller. The reason for these rather paradoxical changes is that because of the wider extent of infarcted and therefore electrically inert muscle, more of the cavity negativity was transmitted to the electrodes in the C_1 and C_2 positions, and hence the (negative) amplitude in these leads is greater than it was when the infarct was smaller. Leads V_5 and V_6 are affected in the opposite way. Being lateral to the actual infarct, they tend to have positive R waves derived from the surviving healthy muscle underlying the exploring electrode. These R waves do not, however, attain their previous amplitude, partly because some of the forces formerly contributing to them had originated in muscle subsequently infarcted, and were accordingly abolished, and partly because the wider transmission of cavity negativity through the more extensive infarct tends to neutralize those that remain. The limb leads, subject to the same influences as Leads V_5 and V_6 , were likewise reduced in amplitude with extension of the infarct.

The examples we have presented have all been from cases of anterior infarction, but it can be shown that posterolateral infarction may affect the limb leads and the leads from the left precordium in similar fashion.

We have pointed out that anterior infarction very frequently leads to low voltage in Leads V_5 and V_6 , but it is not our intention to suggest that it invariably does so or that when it does it is necessarily accompanied by low voltage in the limb leads. For example, the tracings shown in Fig. 3,A and B, are those of a patient with anteroseptal infarction. The precordial leads, B, show all the characteristic QRS changes and yet the deflections of Leads V_5 and V_6 and of the limb leads, A, are of normal amplitude. Lead V_4 , it is true, shows low voltage. Fig. 3,C and D, represents the limb and precordial leads from another case of anterior infarction. In this case Leads V_4 and V_6 do indeed show low voltage, and yet the deflections in the limb leads are quite large. These two cases are included to show how variable are the combinations that can occur in the different leads, and it is emphasized again that while we have indicated certain general relationships between the QRS amplitudes in Leads V_5 and V_6 and those in the standard leads, it is with full realization that these relations are not always present.

Arteriosclerotic Heart Disease: This is another diagnosis which occurred frequently among the cases in this series (Table III). The term does not have a very precise significance and is often used in cases in which the heart does not show any gross abnormality when examined post mortem. On histologic ex-

amination, however, the myocardium may exhibit extensive streaky and patchy replacement of the muscle by fibrous tissue. Each muscle fiber thus replaced represents the loss of a functioning unit normally contributing to the total electromotive force developed by the heart, and the elimination of a large number of such units may well lead to a pronounced reduction in the size of the electrocardiographic deflections through its effect on the mass of the cardiac muscle. An autopsy was performed in only one of the cases of our series falling into this category. Diffuse fibrosis and scarring of the myocardium was found. A pulmonary infarct was also present in this instance.

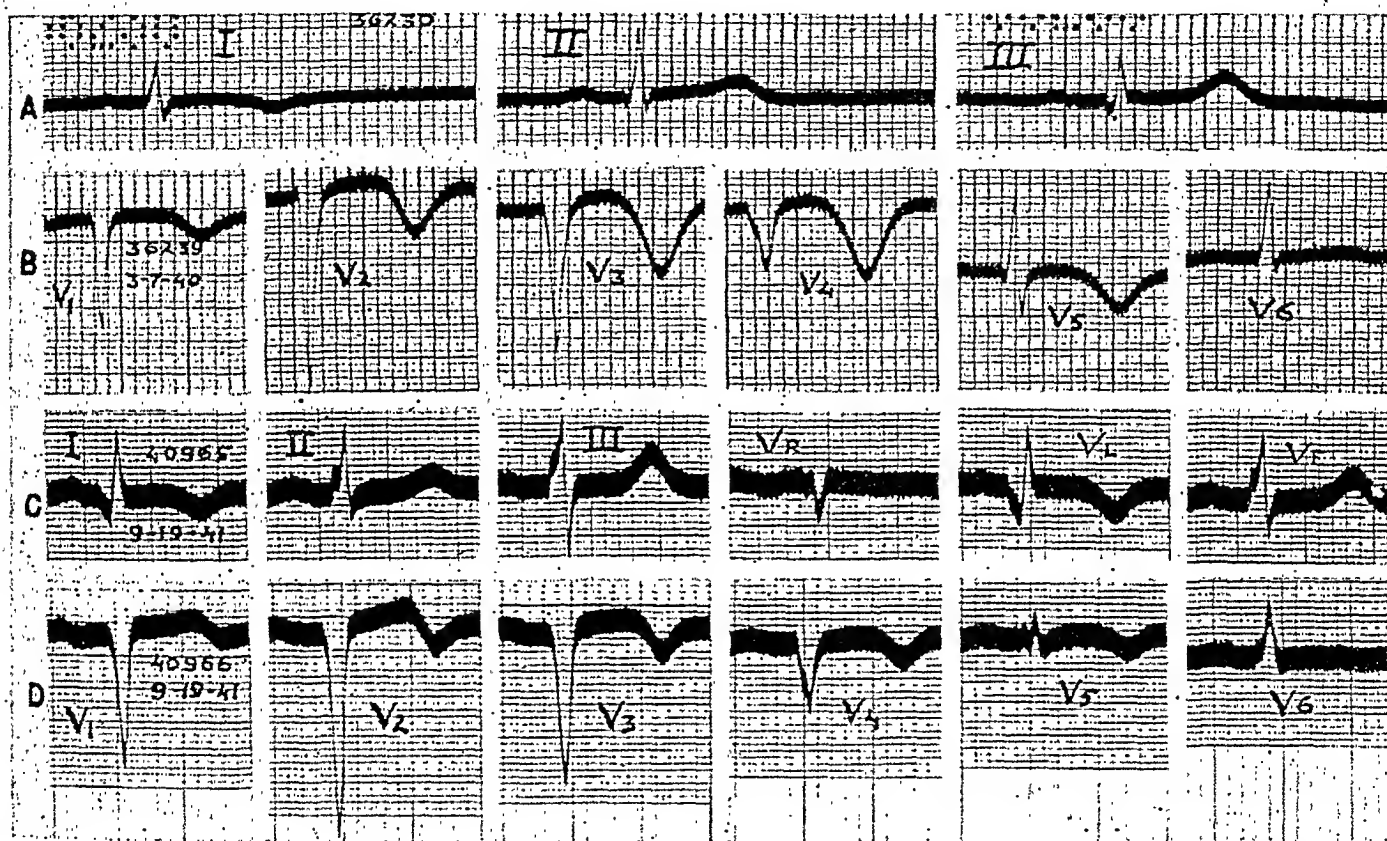


Fig. 3.—A and B, Electrocardiogram of a patient with an anterior infarct, showing normal voltage in Leads V_1 and V_6 and in the limb leads. C and D, Electrocardiogram of another patient with an anterior infarct, showing low voltage in Leads V_1 and V_6 but normal voltage in the limb leads.

Conditions That Affect the Conductivity of the Tissues Surrounding the Heart.—

It will be seen from Table III that after exclusion of the thirty-five cases of myocardial infarction there remain thirty instances of low voltage in one or more precordial leads. In twelve of these the patient had a pleural or a pericardial effusion. There were also six examples of pronounced pulmonary congestion or edema of the lungs, one of marked pulmonary emphysema, and one instance of peripheral edema alone in this group. A number of experimental studies have a bearing upon the manner in which these conditions tend to produce low voltage, even in the absence of primary heart disease.

Eyster and associates²² found that when extensive edema was produced in animals by infusion of the tissues with isotonic salt solution, a conspicuous fall in total body impedance was recorded under certain experimental conditions.

In their impedance experiments, however, these writers employed alternating currents of a frequency (4×10^4 cycles per second) far above any of those found in the electrocardiogram. The bearing of this work upon the impedance offered by the tissues to currents of electrocardiographic frequency is therefore open to serious question. In the experiments of Katz and co-workers,²³ parts of the heart surface were short-circuited by means of lead or tinfoil, or insulated by means of glass and rubber. Both of these procedures naturally reduced the voltage of the electrocardiogram. Since the conductivity of metals on the one hand and of dielectrics, such as glass or rubber, on the other are of an order entirely different from that of tissue or tissue fluid, such experiments probably have little practical bearing on the problems under consideration here.

Theoretically, an increase in the amount of extracellular fluid might be expected to reduce the voltage of the electrocardiogram by its short-circuiting effect upon the cardiac currents, since such fluid, compared to organized tissues, offers a relatively low resistance to low-frequency current. Kaufman and Johnston²⁴ in experiments on animals measured the specific resistances of the tissues surrounding the heart and found values approximately as follows for the different tissues (expressed in ohms per cubic centimeter): muscle, 575; liver, 506; lungs (normal inspiration), 744; lungs (superinflated), 1,227; pericardium, 405; serum, 98; blood, 185; fat, 1,808.

In the healthy individual the tissues chiefly concerned are pericardium, muscle, liver, and normally inflated lung, and the differences in specific resistance between these tissues are sufficiently small to justify the assumption that the cardiac currents are distributed in accordance with the principles that govern current flow in a homogeneous volume conductor.²⁵ Since the specific resistance of serum is only 98 ohms per cubic centimeter, it is probable that collections of fluid near the heart, whether in the form of massive effusion into the pericardial or pleural spaces or of abnormal extracellular accumulations in the alveoli or connective tissue of the lungs (as, for example, in pulmonary congestion or pulmonary edema), have a more or less pronounced short-circuiting effect upon the cardiac currents and reduce the potential variations recorded at the body surface.

On the other hand, air-containing spaces, such as are present in pneumopericardium and pneumothorax, must act as insulators and would be expected to diminish the size of the electrocardiographic deflections in some leads if not in all. In severe emphysema the lung tissue is thin, atrophic, and relatively avascular and the alveolar spaces are abnormally large, so that it may be that in this condition the pulmonary resistance approaches that for superinflated lung, with consequent insulating effect. It must be conceded, however, that without more accurate knowledge of the actual magnitude of the changes in specific resistance that occur under these various circumstances it is difficult to estimate their effects upon the electrocardiogram with any pretense to accuracy.

The smallest precordial deflections observed in our series occurred in the electrocardiogram of a 22-year-old girl with tuberculous polyserositis. This patient had effusions of fluid into the pericardial and left pleural spaces. When the two upper records of Fig. 4 were taken Feb. 24, 1939, both of these had been aspirated and replaced with air. Roentgenographic examination February 23

had been reported as showing air and fluid in the pericardial sac, with marked thickening of the pericardium, and air and fluid in the left pleural space. The QRS deflections in the limb leads were very small (Fig. 4, A), but those of the precordial leads were even smaller. This is the sole instance in which the precordial deflections were smaller than those of the limb leads. The explanation appears to be that the combination of fluid, air, and thickened pericardium interposed between the chest electrodes and the precordium, with the short-circuiting effect of the one added to the insulating effect of the other, largely prevented the transmission of the potential variations of the cardiac surface to

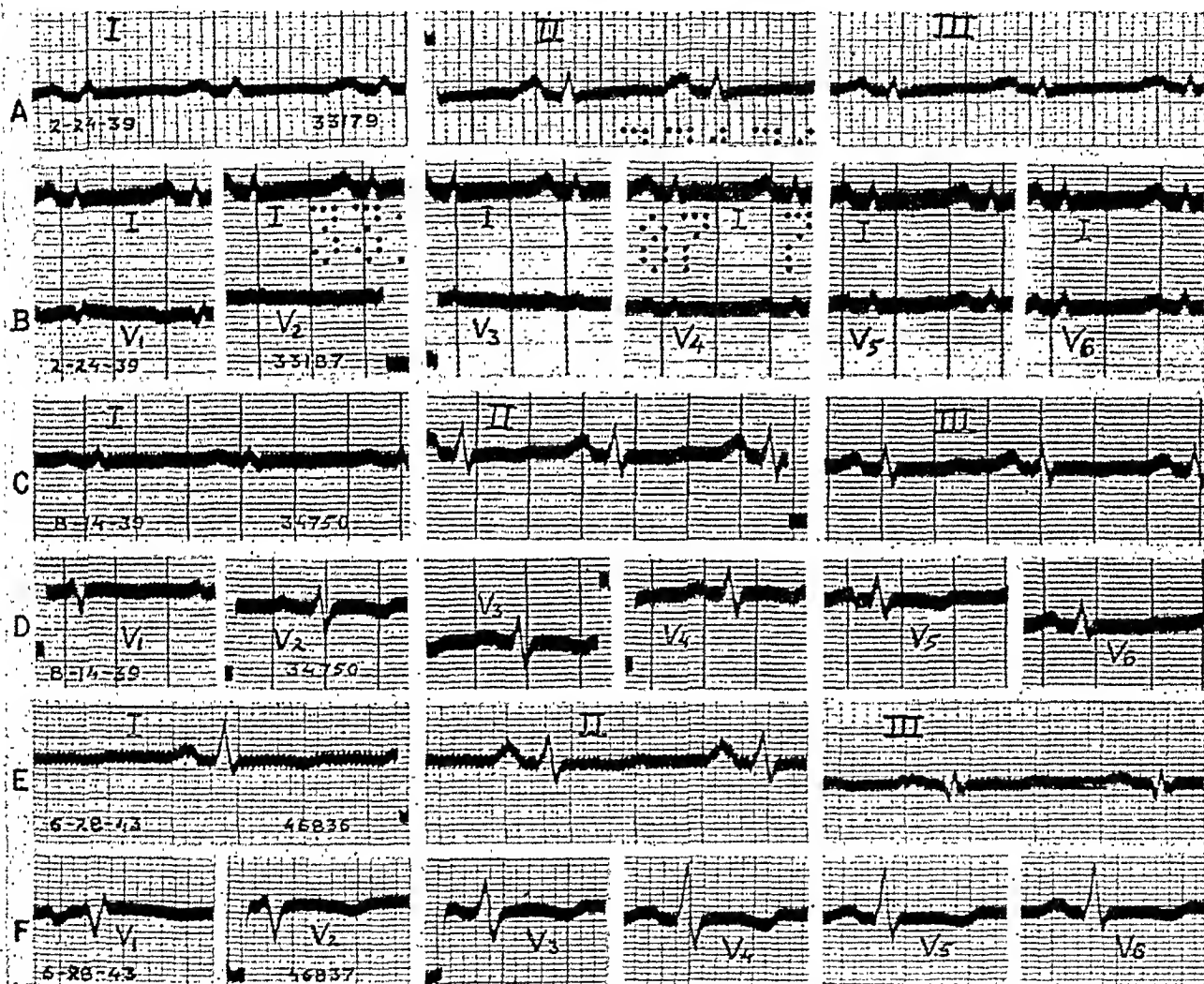


Fig. 4.—Electrocardiograms of a young woman with hydropneumopericardium of tuberculous origin. A and B, Extremely low voltage, especially in the precordial leads, in the presence of air and fluid in the pericardial sac. C and D, Increased voltage after absorption of air from pericardial space; fluid still present. E and F, Further increase in voltage after absorption of fluid.

the precordial electrodes. It is interesting that the smallest deflections occurred in Leads V_2 and V_3 , possibly because with the patient in the supine position the enclosed air lay just beneath the part of the precordium from which these leads were taken. Apparently, the potential variations of the sides and back of the heart were better transmitted to the body surface, for the deflections in Leads V_5 and V_6 and in the limb leads were somewhat larger.

The standard and precordial leads taken Aug. 14, 1939, are shown in Fig. 4,C and D. Roentgenograms taken on this date show that the air but not all of the fluid had been absorbed from the pericardial sac and that the left hydro-pneumothorax was still present. The deflections of the standard limb leads are said to have increased moderately and those of the precordial leads considerably, although both are still decidedly subnormal in size.

The two lowermost records in Fig. 4,E and F, were taken June 28, 1943. Roentgenograms on this date showed the lungs completely expanded and no air or fluid in the pericardial sac. The pericardium itself, however, was 5 to 8 mm. thick, and the roentgenkymogram showed diminished cardiac pulsations. Both limb and precordial leads showed a further increase in the size of the ventricular deflections, but it may be that the extreme thickness of the pericardium still prevented these deflections from attaining normal amplitudes.

Low Voltage With no Pathologic Changes in the Heart or Neighboring Structures.—In our main group of one hundred cases there were six and in the subgroup four patients with no evidence of heart disease, emphysema, or hypothyroidism who were not obese and had no increase in extracellular fluid. In the four last-mentioned cases the clinical diagnoses were (1) minimal pulmonary tuberculosis, arrested; (2) adenocarcinoma of the stomach; (3) neurocirculatory asthenia; (4) no disease. The last two cases will be discussed in detail below. As to the manner in which low voltage is produced in such cases, we can offer only some speculations which leave much to be desired.

The size of the deflections in the standard limb leads depends not upon the total electromotive force generated by the myocardium but upon the projection of this electromotive force, considered as a vector, upon the frontal plane. This component is large when the spatial electrical axis is nearly parallel and small when it is nearly perpendicular to this plane. Otto²⁵ demonstrated this experimentally by rotating the heart forward on a basal transverse axis. He found that the deflections in the limb leads were largest when the apex was most caudad and became progressively smaller as the apex was tilted anteriorly and cephalad. They were smallest when the long axis of the heart was perpendicular to the frontal plane.

Meek and Wilson²⁷ rotated the canine heart about its longitudinal and antero-posterior axes and produced marked alterations in the position of the cardiac electrical axis. In this way they obtained either pronounced left or pronounced right axis deviation with corresponding variations in the size of the ventricular deflections.

Cohn and Raisbeck²⁸ used another approach to the same problem. Instead of displacing the heart itself, they ingeniously rotated the apices of the "Einthoven triangle," and therefore the directions of the standard limb leads, through 360 degrees in the frontal plane. By this method they were able, both in the case of subjects with normal and those with hypertrophied hearts, to obtain tracings depicting either extreme right or extreme left axis deviation.

These and other experiments indicate that position of the cardiac electrical axis and the size of the deflections in the limb leads are determined, to a large

extent, by such factors as the position of the heart and the contour, symmetry, and thickness of the chest wall. In certain cases similar factors probably explain the occurrence of unusually small deflections in the precordial electrocardiograms of subjects who show no other evidence of disease. Thus low voltage is common in Leads V_3 or V_4 when these are from points in the transitional zone where the potential variations of one ventricular surface tend apparently to cancel those transmitted from the other.

There are cases, however, in which most or all of the precordial leads exhibit low voltage, and it is not easy to explain exactly how this happens. Two cases in our series fall into this category. Both displayed unusual features in addition to the low voltage and presented some initial diagnostic difficulties.

CASE 1.—T. M., a young woman, 31 years of age, complained of palpitation, dizziness, vague pains in the chest, choking sensations, and a feeling that she could not get enough air at each breath. There was no history of rheumatic or scarlet fever and there had been no dyspnea or edema. Physical examination was entirely negative; the body habitus was asthenic, the blood pressure 12/88, the heart sounds normal. There was no edema, no pulmonary congestion, no emphysema, no evidence of hypothyroidism. The teleroentgenogram was normal. The final diagnosis was psychoneurosis and neurocirculatory asthenia. The electrocardiogram is shown in Fig. 5. The upper record shows the standard limb leads and unipolar extremity potentials. Low voltage is present in all these leads and the T wave is rather flat in Lead I. The precordial leads are shown in the middle record. The RS deflection is rather small in all leads; it is largest in Lead V_4 , in which it measures only 1.0 millivolt. There is inversion of the T wave in Leads V_1 , V_2 , and V_3 . Inverted T waves are commonly found in Lead V_1 in normal persons and occasionally in Lead V_2 , but after early childhood they are very uncommon in Lead V_3 . The lower record shows the precordial leads after the administration of amyl nitrite. The T wave has become diphasic in Lead V_2 and upright in Lead V_3 , without a conspicuous change in heart rate.

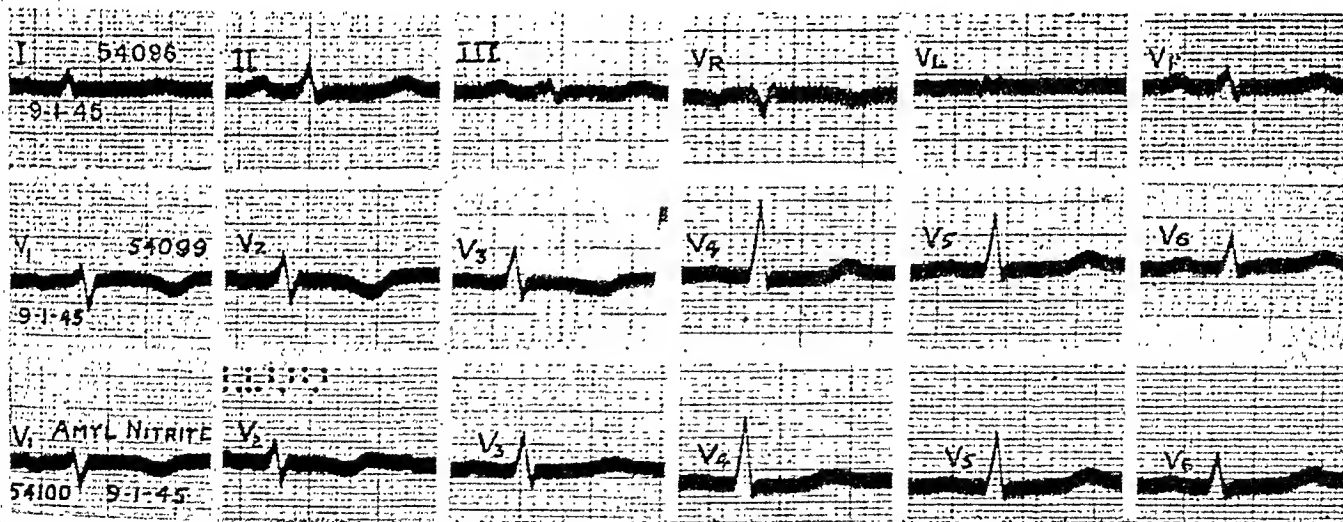


Fig. 5.—Electrocardiogram of a young woman with neurocirculatory asthenia, showing low voltage in almost all leads, flat T waves in Lead I, and inverted T waves in Leads V_2 and V_3 . Lowest record shows tendency for T waves to become upright in Leads V_2 and V_3 after administration of amyl nitrite.

Inversion of the T wave in both the standard and precordial leads in cases of neurocirculatory asthenia, with reversion of the electrocardiogram to normal after the administration of ergotamine tartrate or of amyl nitrite, has been the subject of several recent studies.³⁰ It was of particular importance to recognize the benign nature of the T-wave changes in this case, for the combination of

low voltage and inverted T waves in the electrocardiogram of a patient with complaints referred to the cardiovascular system might have led to an erroneous and mischievous diagnosis of serious heart disease with resulting intensification of the cardiac neurosis already present.

CASE 2.—C. B., an Army medical officer, 30 years of age, was thought by his associates to be somewhat cyanotic about the lips and nail beds while he was testifying before a medical review board. Apart from the tension and anxiety natural to the situation, there were no subjective symptoms. He had always been strong and healthy, of athletic habits and physique; there was no history of rheumatic or scarlet fever or of diphtheria. There had been no undue dyspnea or chest pain, nor indeed was the cyanosis ever noted again. Physical examination and a teleroentgenogram showed no abnormalities and no further attention would have been paid to the episode had it not been for the electrocardiogram, which showed low voltage in the standard limb leads with inverted T waves in Lead I (Fig. 6, A). The precordial leads (Fig. 6, B) show normal voltage in Leads V₁, V₂, V₃, and V₄ but low voltage in Leads V₅ and V₆. The QRS complexes are of normal configuration, and the low voltage in the standard limb leads and in the leads from the left precordium, with normal voltage in the remaining precordial leads, could have resulted merely from a shift in the direction of the mean electrical axis toward the sagittal plane, in the absence of heart disease. The inverted T waves in Leads I, V₃, V₄, V₅, and V₆, however, also required explanation. Fig. 6, C shows the effect of exercise on these T waves in Leads V₄ and V₅. The control record was taken with the subject standing; Leads V₄ and V₅ show inverted T waves as previously. The same leads were then recorded, with the subject again in the upright position, but immediately after he had stepped briskly up and down a standard two-step stairway fifty times. In this record the T waves in Leads V₄ and V₅ are upright. Five minutes later a third record was taken, and the T waves in these leads were again both negative.

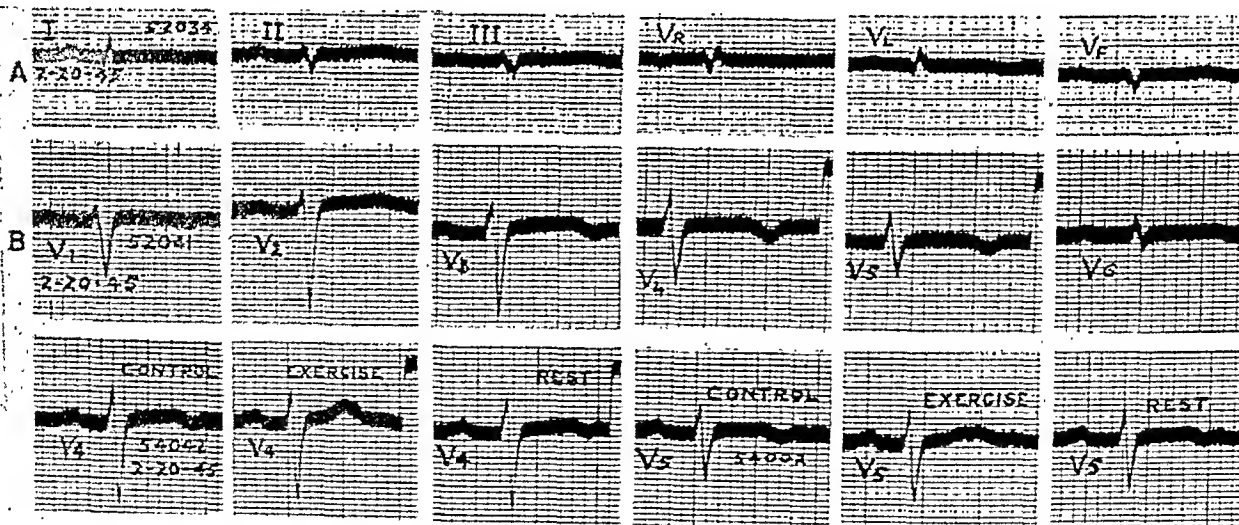


Fig. 6.—Electrocardiogram of an apparently healthy young man. A, Low voltage and flat T waves in the limb leads. B, Low voltage in Leads V₅ and V₆ and inverted T waves in Leads V₃, V₄, and V₅. C, Effect of exercise: T waves in Leads V₄ and V₅ become upright immediately after exercise and then revert to negativity with rest.

As in the previous case, the inconstant T-wave inversion was regarded not as a sign of disease but as a physiologic variant apparently related in some way to an unstable balance between sympathetic and vagal tonus. Whether or not this conclusion was correct is uncertain; the patient's health two years after the electrocardiographic peculiarity was first noted is still excellent.

Low Voltage of P and T Waves.—In a paper already referred to, Wilson²¹ suggested that the QRS deflections might be low in the electrocardiograms of some normal persons because the electrical forces produced by one part of the heart were neutralized by those arising in other parts. In this case, he reasoned, the P wave and perhaps the T wave should be of normal amplitude. On the other hand, when the QRS deflections were diminutive because of altered tissue conductivity or myocardial degeneration, then the P and T deflections should also be small.

In this study the P and T deflections were classified as showing low voltage if both were less than 0.1 mv in amplitude in all three of the standard limb leads. In our total group of one hundred cases with low voltage of QRS in the limb leads, small P and T deflections occurred in thirty patients. Thirteen of the patients concerned had hydrothorax or hydropericardium and twelve had marked congestion of the lungs with or without peripheral edema. The remaining five had no extracellular fluid accumulations.

DISCUSSION

Several conclusions are suggested by an analysis of our cases and the comparison of our data with those collected by other investigators.

1. The electrophysiologic factors that produce low voltage in the standard limb leads tend to produce low voltage in the precordial leads also. This might be expected a priori, but certain authors¹⁴ were led to the conclusion that, with few exceptions, no conditions other than severe myocardial disease produced low voltage in the precordial leads. Our own series, like theirs, is biased by the method of sampling used, for most of the subjects included in it must have been suspected of having myocardial disease before the electrocardiogram was ordered. It is not surprising, therefore, that most of them did have serious organic disease. Nevertheless, a certain number were found not to have heart disease and some had no organic disease of any kind.

2. It is very uncommon to find extremely low voltage in all six precordial leads even in the presence of extensive disease. Most often, when the deflections in the standard limb leads are small, those of the leads from the left side of the precordium are also small, since both reflect forces acting in the frontal plane. The forces acting in the sagittal plane may actually be very large in some of these cases, and this is suggested by the occurrence in some instances of large deflections in leads from the midprecordium, such as Leads V_2 and V_3 . These sagittal forces are almost without effect upon the standard limb leads.

3. In the diagnosis of myocardial disease the configuration of the QRS deflections is of far greater significance than their size.

SUMMARY AND CONCLUSIONS

1. Low voltage occurred in one or more of precordial Leads V_2 to V_6 in sixty-five of one hundred cases selected because of the occurrence of low voltage in the limb leads.

2. Low voltage occurred in all six precordial leads in three cases only. It was most frequent in Lead V_6 (fifty-six cases) and least frequent in Lead V_2 (three cases).

3. In most instances in which certain leads showed low voltage, the size of the deflection of other leads was well within normal limits, and in many the chief deflection in the lead in which the voltage was largest was distinctly greater than the average for its kind. The largest deflection occurred most often in Lead V_2 in contrast to the normal situation in which it is most frequent in Lead V_4 . This suggests that in our series the mean electrical axis, on the average, was shifted toward the sagittal plane.

4. By far the greater proportion of the patients in this series had serious heart disease. Myocardial infarction was present in thirty-five and arteriosclerotic heart disease in fifteen of the sixty-five cases. The manner in which these conditions may produce low voltage in certain leads is discussed in the text.

5. Low voltage did occur, however, in both precordial and limb leads of some patients with no intrinsic disease of the heart. Most of these had extracardiac disorders of a type that would be expected to change the electrical conductivity of the tissues surrounding the heart.

6. Low voltage also occurred in both standard limb leads and precordial leads of a small number of persons who exhibited no evidence of physical disease. In such cases it is probably the result of an unusual orientation of the anatomic and hence of the mean electrical axis of the heart.

The writer wishes to express his gratitude to Dr. Frank N. Wilson for his many valuable suggestions and for his help in the preparation of this paper.

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WEIGHT OF THE RED BLOOD CORPUSCLES IN HEART FAILURE DETERMINED WITH LABELLED ERYTHROCYTES DURING AND AFTER DECOMPENSATION

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IN DETERMINING the volume of the circulating blood, one can, in principle, employ substances which display a particular affinity either for blood corpuscles or for plasma. Dyes are an especially useful example of the latter variety of substance and were first introduced for this purpose by Keith, Rowntree, and Geraghty in 1915.¹ Recently blue azo dye, T-1824, has been most frequently employed, the method having been devised by Dawson, Evans, and Whipple² in 1920. This dye has been used in particular by Gibson and Evans³ in their clinical studies. It is injected into the circulation and its concentration is then determined colorimetrically in samples of blood. The concentration curve presents two phases: in the first phase there is a rapid fall in concentration during the first three to six minutes (the mixing curve); the second phase consists of a more gradual fall in concentration (the disappearance slope). Equilibrium is considered to exist at the point where the first phase merges into the second. In fifteen normal cases, Gibson and Evans found that equilibrium was reached seven and one-half minutes after the injection of the dye, whereas Gregersen,⁴ who has used this method to study many problems of the circulation, found the corresponding time to be nine minutes. The plasma volume is obtained by extrapolating from the point of equilibrium to the zero level. The mixing curve is due to the mixing of the dye with the blood, while the disappearance slope has been found to depend on the fact that blue azo dye, which is adsorbed on the serum albumin, diffuses out into the tissues and is partially removed by the reticulo-endothelial system. In 1940, Cardozo⁵ showed that fifteen to thirty minutes after the injection of the dye into the blood stream the lymph began to acquire a blue color and that two hours after injection the concentration of the dye in the lymph was 40 per cent of its concentration in the plasma. The choice of a point of equilibrium is thus arbitrary. The volume of the circulating blood corpuscles is calculated from the hematocrit reading and the plasma volume. The method has been freely criticized, most recently by King, Cole, and Oppenheimer⁶ and by Gregersen and Rawson.⁷

The method in which the cellular volume is determined first differs in principle from the dye method which we have just discussed. In 1882, Gréhant

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and Quinquaud⁸ introduced carbon monoxide for this purpose in experiments on animals. The method has since been modified for clinical use on various occasions by Salvesen,⁹ Haldane and Smith,¹⁰ van Slyke and Robscheit-Robbins¹¹ and Asmussen.¹⁷ Most of the investigators who have made use of the carbon monoxide method have had the subject breathe in a closed system for varying periods: Haldane and Smith,¹⁰ for two to three minutes; Arnold, Carrier, Smith, and Whipple,¹² for four minutes; McIntosh,¹³ Steinmann,^{14,15} Plesch,¹⁶ and Grosse-Brockhoff and Molineus,¹⁷ for about nine minutes; and Chang and Harrop¹⁸ for as many as twenty minutes. Blood samples were then taken and their carbon monoxide content determined either by the van Slyke method of gas analysis or by Haldane's carmine titration method, with a spectrometer, or by the photoelectric method of von Hartmann¹⁹ and Steinmann.¹⁴ Van Slyke and Robscheit-Robbins¹¹ have employed another method; they have injected blood saturated with carbon monoxide intravenously and have then determined by gas analysis the concentration in samples taken four minutes later. Most of the investigators mentioned estimate the margin of error at about 5 per cent.

The carbon monoxide method has been criticized on the following grounds, among others. Since carbon monoxide is a poison, its concentration in the blood must be kept very low in cases of cardiac insufficiency or anemia. The purity of the carbon monoxide must be determined before inspiration. The amount of carbon monoxide remaining in the closed system, which is estimated at 1 to 2 per cent, must also be taken into account. Steinmann¹⁴ has also pointed out that the blood carbon monoxide in habitual smokers may range between 0 and 5 per cent, and, must, therefore, be determined before the experiment. The patient must take an active part in the experiment; this may be difficult in cases of cardiac insufficiency. A very important consideration is the fact that a certain amount of the carbon monoxide, estimated at 5 per cent, is taken up by the myoglobin and leaves the blood stream. Haldane and Smith¹⁰ have also drawn attention to another small source of error: the fact that 0.3 per cent carbon monoxide can be physically dissolved in blood. For all of these reasons, the blood carbon monoxide tends to fall, and one cannot obtain a reliable equilibrium level. The calculated volume of the blood corpuscles, therefore, tends to be too high.

Smith, Arnold, and Whipple²⁰ carried out comparative determinations of the blood volume in dogs with Welcker's method, the carbon monoxide, and the blue azo dye method and found that the plasma method gave the largest blood volume, whereas the Welcker and the carbon monoxide methods gave approximately the same results. These authors also have discussed the principle of the hematocrit and have expressed the view that its reading is too high when the blood sample is taken from the jugular vein, the reason being that the proportion of plasma to blood corpuscles varies in vessels of different caliber. Stead and Ebert²¹ state that a hematocrit reading of 40 to 50 for the jugular vein is about 25 per cent higher than the cellular volume obtained by direct determination, as, for example, by the carbon monoxide method. Similar views have been expressed by Hahn, Ross, Bale, Balfour, and Whipple²² and by Fåhræus.²³ By comparing the circulating blood volume, as determined by the plasma method and hemato-

crit, with the volume as determined by the carbon monoxide method and hematocrit, Bazett, Sunderman, Maxfield, and Scott²⁴ and others have found that the former method gave the larger figure. These investigators, as well as Smith, Arnold, and Whipple,²⁰ recommend a combination of the carbon monoxide and plasma methods for determining the circulating blood volume.

The introduction of radioactive isotopes appears to have provided a method for determining the volume of circulating blood corpuscles in which mixing with the blood is rapid and equilibrium is maintained for fifty to sixty minutes with radioactive phosphorus (according to Nylin) or for weeks with radioactive iron (according to Hahn, Bale, and Balfour²⁵). Hevesy and associates²⁶⁻²⁸ have devised an excellent method of labelling the red blood corpuscles with radioactive phosphorus, with the help of which Nylin,³⁰⁻³² and Nylin and Malm²⁹ have carried out a number of clinical investigations. Nylin has pointed out that it is important to observe the process of dilution by means of repeated tests during a considerable period. When the dilution curve is known, it is possible to determine in any particular case at what point equilibrium is established and to calculate the volume of the circulating blood. This method also enables one to carry out valuable investigations during the period in which equilibrium is maintained. Nylin and Malmström³³ and Gernandt and Nylin³⁴ have previously measured the circulation time with decholin and have found that the prolonged circulation time and the persisting sensation of taste in compensated patients with dilated hearts are closely correlated with the amount of residual blood in the heart. Nylin has since verified this by using red blood corpuscles labelled with radioactive phosphorus.

Hevesy, Køster, Sørensen, Warburg, and Zerahn³⁵ have employed similar methods in their physiologic studies on normal subjects. They have compared the volume of circulating blood, as determined with radioactive phosphorus, with that determined by carbon monoxide and have found the latter to be 30 per cent higher, largely because of the action of myoglobin in taking up carbon monoxide. Brown, Hempelman, and Elman³⁶ and Hahn and Hevesy^{26,27} have employed another method of determining the blood corpuscular volume in dogs and rabbits, respectively, with radioactive phosphorus. These investigators first inoculate a donor animal and then inject its activated blood into the experimental animal whose blood volume is to be measured. The same procedure has also been used by Anderson.⁴⁶ A donor must also be used when the circulating blood volume is determined with radioactive iron.^{22,25,37,38} The investigators who have employed this method have also found that the cellular volume determined with radioactive iron is about 25 per cent smaller than that determined from plasma volume with blue azo dye and the hematocrit. It thus appears that radioactive isotopes are particularly suitable for determining the volume of circulating blood corpuscles.

Relation of Blood Volume and Heart Failure.—A knowledge of the variations in the blood volume in cases of cardiac insufficiency has been found to contribute to an understanding of the mechanism involved in the development and elimination of decompensation. The fluctuations in blood volume have been correlated

with other clinical observations during the decompensation and after the administration of digitalis. Wollheim³⁹ employed the trypan red method to determine the total volume of blood in a large number of clinical cases and has found the normal value to be 5,330 c.c., or 83.9 c.c. per kilogram of body weight.* The average volume of circulating blood in decompensated patients with edema was found to be 5,890 c.c., or 84 c.c. per kilogram of body weight. The range was from 74 to 120 c.c. per kilogram of body weight. After compensation was restored, this fell to an average value of 4,990 c.c., or 70.0 c.c. per kilogram of body weight. The range was from 56 to 76 c.c. per kilogram of body weight. Ewig and Hinsberg⁴⁰ employed a combination of the carbon monoxide and plasma methods, as well as the carbon monoxide method alone, and found an increase in the blood volume in decompensation (6 to 7 liters). They found that administration of digitalis caused a considerable reduction in volume to approximately the normal value, or approximately 4.5 liters. Gibson and Evans,³ using blue azo dye, observed an increase in both blood and erythrocyte volume in decompensation, the former amounting to between 22 and 50 per cent in the various stages of insufficiency. They observed a reduction in the whole blood volume after compensation was restored in all cases and a reduction in the corpuscular volume in most cases; the former fell about 1 liter, and the latter, in certain cases, about 500 cubic centimeters. They also observed that a reduction in the plasma volume preceded the fall in cellular volume. Plesch,¹⁶ using the carbon monoxide method, also observed an increase in the whole blood volume and total hemoglobin in decompensation, while Schürmeyer⁴¹ and Steinmann,¹⁵ using the same method, found that the increased blood volume fell after administration of digitalis. Seymour, Pritchard, and Longley,⁴² using blue azo dye, observed a 25 per cent reduction in volume after digitalis. Meneely and Kaltreider⁴³ studied fifteen decompensated patients and observed a 46 per cent increase in the whole blood volume and a 48 per cent increase in cell volume. In three patients in whom compensation was restored, they observed a fall in both. Using blue azo dye, Waller and Blumgart⁴⁴ determined the blood volume in five cases of decompensation and found it to be 125 to 220 per cent of the normal. In every case, the volume fell after the restoration of compensation. Ehrström⁴⁵ obtained similar results with congo red. In a previous investigation, Nylin³¹ found that the erythrocyte volume, determined with radioactive phosphorus, fell by 18 per cent when compensation occurred, the corresponding fall in the whole blood volume being 28 per cent.

METHODS

With a view to studying more closely the variations in the volume of the red blood corpuscles during the various stages of decompensation and after its elimination, we determined the volume of the erythrocytes in a number of patients by labelling them with radioactive phosphorus. Clinical progress during administration of digitalis was observed by means of a routine physical examination and determination of weight, diuresis, pulse frequency, circulation time, venous

*The range in these normal cases was from 75 to 85 c.c. per kilogram of body weight.

pressure, and heart volume by x-ray. In addition to repeated estimations of serum protein, phosphatase, citric acid, Takata, serum bilirubin, hemoglobin, and red blood corpuscles, we determined the diameter of the blood corpuscles and their resistance as well as the degree of reticulosis in various stages of cardiac insufficiency.

In this investigation, the corpuscular volume was determined by the method which was employed in previously published work.²⁹⁻³² Following the procedure described by Hahn and Hevesy^{26,27} and Hevesy and Zerahn,²⁸ red blood corpuscles from the patient were activated with 0.03 mc. of radioactive phosphorus by two hours' shaking in a thermostat at 37° C. Four milliliters of the labelled blood (the plasma was, of course, also activated) were injected into a vein in one of the patient's arms. After the injection, samples of venous blood were taken from the other arm at suitable intervals and centrifuged. The activity of the erythrocytes, and sometimes that of the plasma as well, was then determined with Geiger-Müller equipment. The weight of the circulating blood corpuscles was then calculated from the formula $X = A \times B$ where X is the weight of the erythrocytes in grams, A the weight of labelled corpuscles injected, and B the proportional relationship between the specific activity of the injected labelled corpuscles and the average specific activity of the blood corpuscles taken from samples in which equilibrium has been established. In converting the weight of the erythrocytes in grams to their volume in milliliters, the specific gravity of the corpuscles was taken to be 1.08, as given by Hevesy. A fuller account of the procedure and its sources of error was given in previous papers by Hevesy, Zerahn, and Nylin.

The volume of the plasma and of the whole blood in circulation was then calculated from the volume of the erythrocytes and the hematocrit reading. We are fully aware that a hematocrit reading, based on blood taken from an arm vein, does not indicate the true proportion between blood corpuscles and plasma in the circulation as a whole; we have referred to this earlier. The figures which are given for plasma volume and total circulating blood volume are given only for purposes of comparison with earlier investigations.

The hematocrit reading was carried out in accordance with the procedure originally described by Hedin.⁴⁸ The blood samples were centrifuged in capillary tubes at 6,000 revolutions per minute for thirty minutes. Heparin was used as an anticoagulant (Ponder,⁴⁹ Millar⁵⁰). The venous pressure was measured in the manner described by Moritz and Tabora,⁵¹ and the radiologic estimation of the heart volume was determined by the method advised by Liljestrand, Lysholm, Nylin, and Zachrisson.⁵⁰

RESULTS

Nineteen patients, none of whom had any disorder of the blood or circulation, provided material for twenty-one determinations of the normal corpuscular volume and whole blood volume by the method which has been described. Six were healthy men in good training; six patients were being treated for gastric ulcer or gastritis; two patients were given the diagnosis of chronic polyarthritis; one, chronic nephritis; one, spondylosis deformans; one, neurosis; one, acute

pulmonary tuberculosis; and one, acute pleurisy. We found the average weight of the blood corpuscles to be 2,100 grams, or 31.2 grams per kilogram of body weight. The latter figure, 31.2 grams, is lower than the figure of 36.0 grams found by Hevesy, K ϕ ster, S ϕ rensen, Warburg, and Zerahn³⁵ in twenty-two subjects. There was an unmistakable correlation between the weight of the blood corpuscles and the body weight; heavy, muscular patients possess more blood corpuscles than thin ones (Fig. 1).

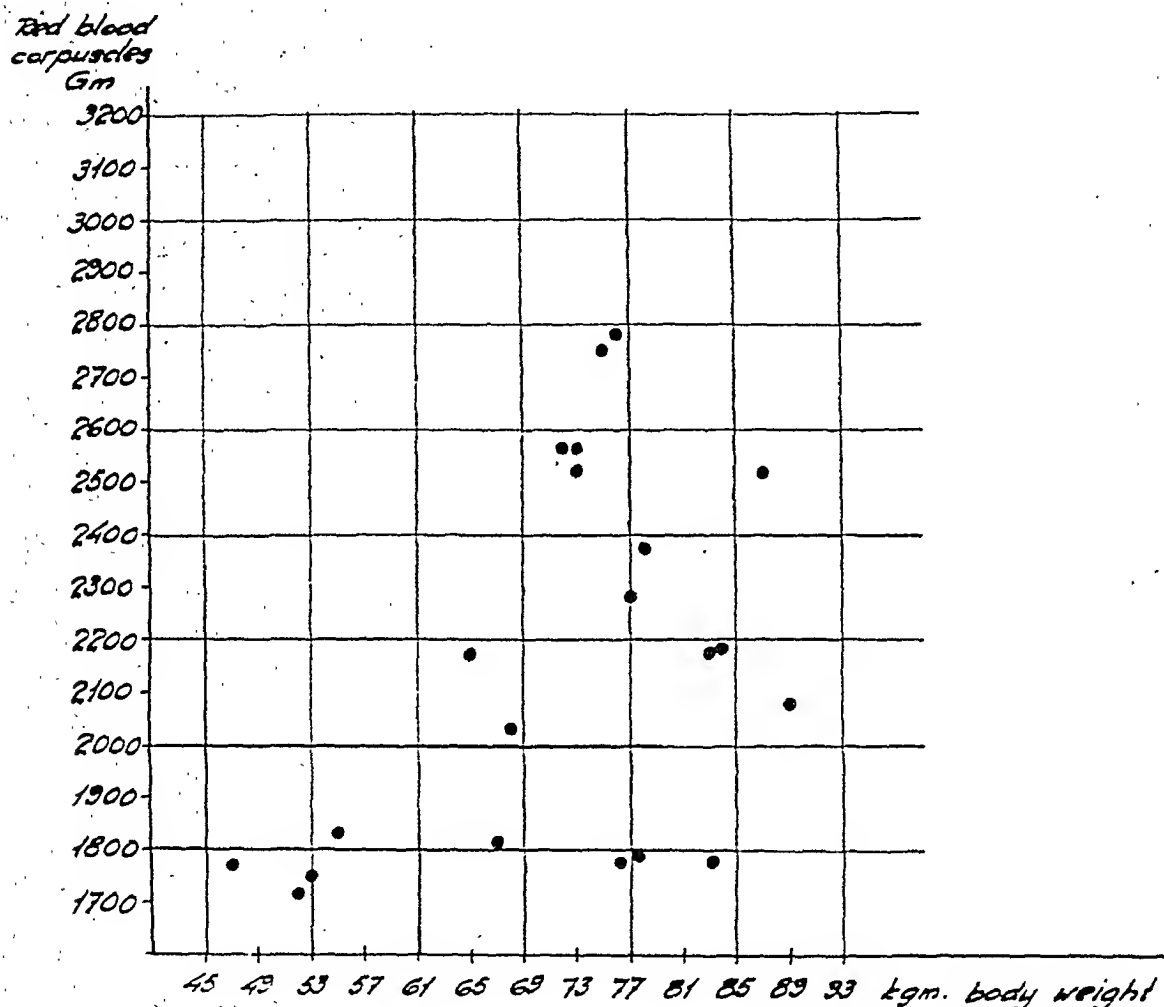


Fig. 1.—Correlation between body weight and the weight of red blood corpuscles in normal cases.

As previously mentioned, Nylin and associates have shown that the circulation time (determined with the decholin method) in cardiac insufficiency indicates not only the degree of congestion, but also, to a large extent, the dilatation of the heart and, therefore, the amount of residual blood remaining in it. Statistical analysis of a large number of cases has shown that there is a definite correlation between the radiologic volume of the heart and the circulation time in compensated cardiac disease. With a view to investigating this matter more closely, Nylin has, as reported in previous papers, measured the circulation time by labelling red blood corpuscles with radioactive phosphorus by the method which has been described. If one studies the dilution curve of the blood of normal individuals after injection of the labelled corpuscles, one finds that the activity is measurable after ten to fifteen seconds, that it reaches a maximum after twenty

to twenty-five seconds, and that equilibrium is established after sixty seconds and maintained for about one hour. There is found to be close agreement between the circulation time determined by the decholin method and that obtained by labelling erythrocytes with radioactive phosphorus. In cardiac cases, on the other hand, the dilution curve is different.

Fig. 2 shows a case of this kind. The patient was a 48-year-old man with mitral stenosis who was completely compensated. The venous pressure was 10.5 cm. and the circulation time, 25 to 79 seconds as determined with decholin. The first sensation of taste was thus delayed and its total dura-

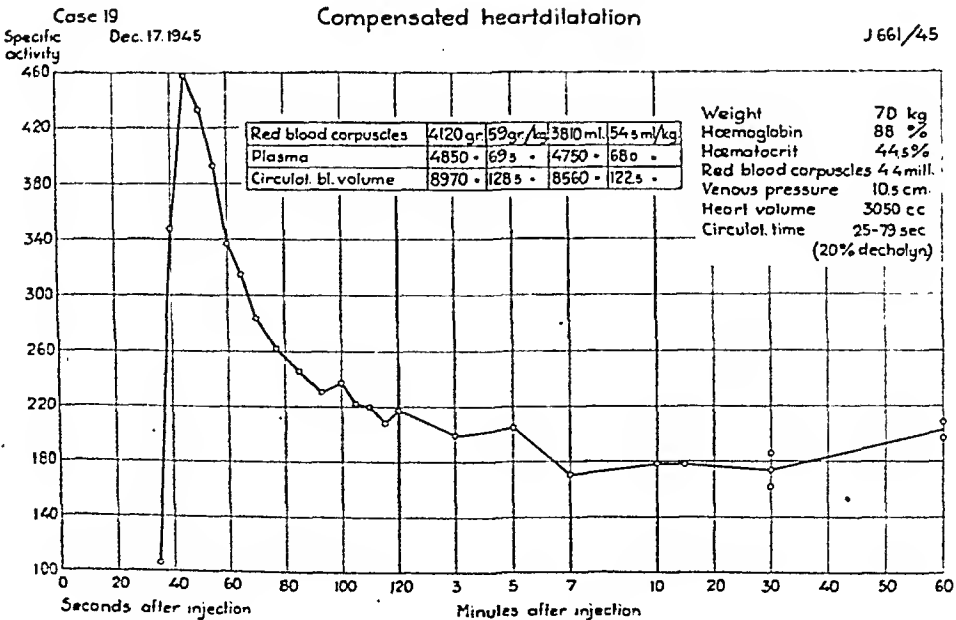
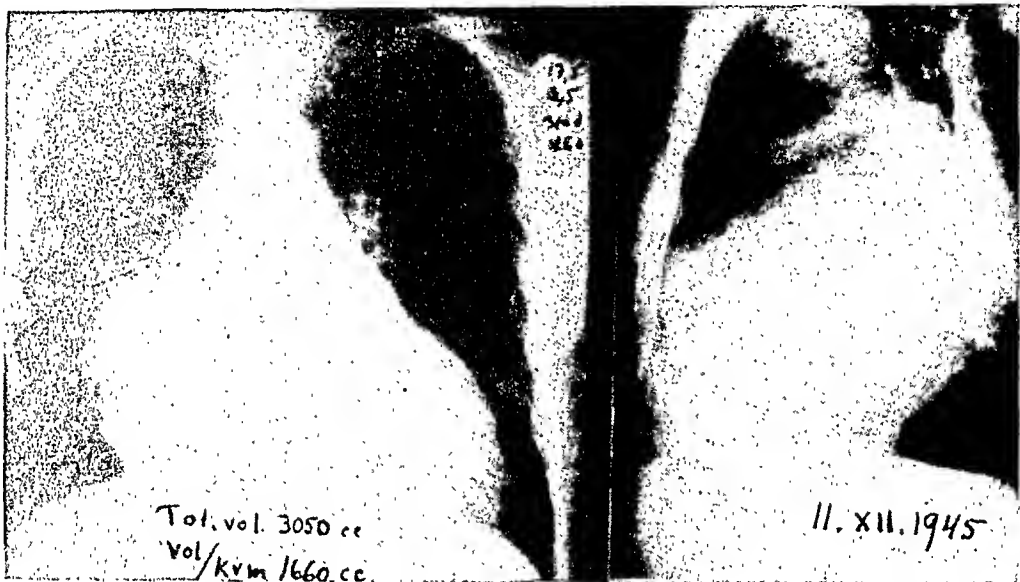


Fig. 2.—Results obtained in a 48-year-old man with mitral stenosis. Equilibrium was not established until seven minutes after injection of the labelled corpuscles. The curve was therefore shifted to the right.

tion prolonged. The heart was very large; its radiologic volume was 3,050 cubic centimeters. The dilution curve, based on the activity of arterial blood, differed clearly from the normal. The first measurable activity was delayed (thirty-five seconds) and the maximum likewise delayed (fifty seconds), and equilibrium was not established until after seven minutes. The whole curve has thus been displaced to the right. Between the thirtieth and sixtieth minute, the patient ate a light meal and took a short walk. The result was an increase of about 10 per cent in the specific activity of double samples taken at the sixtieth as compared with the thirtieth minute. This may have been a true increase due to the fact that some labelled blood had been held up in the dilated heart or in some organ where the circulation was particularly slow and partial stasis had occurred. This labelled blood may have reached the vein from which the samples were taken later than the rest of the labelled blood. We will return to this question later.

Our method involves the activation of both corpuscles and plasma, and we inject this activated blood into the subject without centrifuging away the plasma. This is done because we have found that the activity of the plasma falls very rapidly without affecting the activity of the corpuscles. Fig. 3 is based on an experiment of this kind. It shows that the activity of corpuscles and plasma

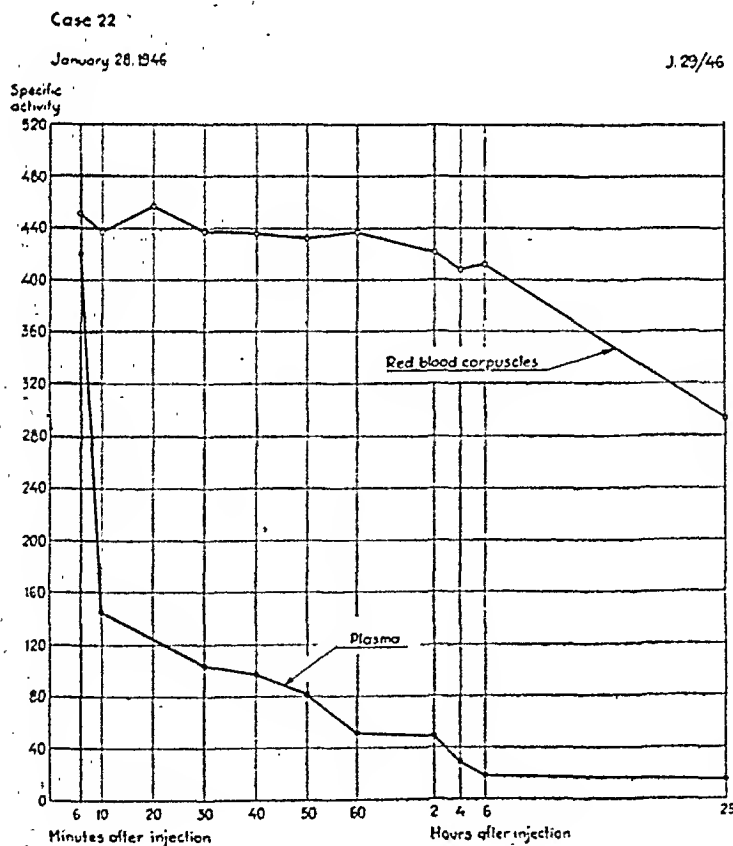


Fig. 3.—Specific activity of red blood corpuscles and plasma during twenty-four hours after intravenous injection of tagged erythrocytes and plasma.

was the same at the end of six minutes. Four minutes later, plasma activity had fallen 65 per cent, and, after sixty minutes, it was only 10 per cent of its original value. The activity of the corpuscles, on the other hand, remained con-

stant throughout. Our procedure involves, therefore, a considerable simplification of the method.

Using the method which has been described, we determined the corpuscular volume and whole blood volume of seven patients in various stages of decompensation and after recovery from it. The patients were also subjected to thorough clinical examinations which included the determination of venous pressure, circulation time, and heart volume.

The diagnoses were as follows: mitral stenosis in three patients, cardiosclerosis in two patients, hypertension in one patient, and aortic regurgitation in one patient.

CASE 21.—A 65-year-old man with cardiosclerosis and auricular fibrillation displayed, on admission, extensive edema and hydrothorax and was severely dyspneic. The venous pressure was 13 cm. H₂O and the heart was considerably dilated (Table I and Fig. 4). The weight of the erythrocytes was found to be 2,820 grams, or 25 grams per kilogram of body weight. This corresponds to 30 grams per kilogram of dry body weight; that is, body weight after elimination of edema. The whole blood weight was 7,550 grams and the plasma weight 4,730 grams. Rest in bed resulted in the loss of 15.6 kilograms of weight and in a fall of venous pressure to 8 centimeters. Examination after rest showed the plasma weight to be 3,850 grams and the whole blood weight 6,680 grams. The reduction is natural in view of the amount of fluid the patient had lost. The corpuscular weight remained the same: 2,830 grams. After further treatment with digitalis, complete compensation was restored and there was a considerable reduction in the volume of the heart (it still remained somewhat dilated) and a fall in the venous pressure to 6 cm. of water. The plasma weight fell to 3,340 grams and the whole blood to 5,600 grams. The corpuscular weight, therefore, was 2,260 grams, or 24 grams per kilogram of dry weight, a reduction of 570 grams, or 20.2 per cent. The change in the proportion of corpuscles to plasma in connection with the removal of fluid is illustrated by the rise in the hematocrit reading from 36 to 40 per cent between the two first estimations, and by the rise of hemoglobin from 70 to 75 per cent and the increase in erythrocytes from 3.6 to 3.9 million. At the third examination, the weight of both erythrocytes and plasma was found to have fallen by about the same amount, but the hematocrit reading remained 40 per cent. The hemoglobin, however, was found to have risen to 79.5 per cent and the red blood corpuscles to have increased to 4.3 million.

A detailed analysis of the various specific activity graphs plotted at different times reveals certain interesting points. Thus, in the examinations on Feb. 11, 1946, and Feb. 25, 1946 (shown in Fig. 4), one sees that the activity of the samples increased during the first ten minutes before becoming fairly constant. This is probably an indication that the labelled blood corpuscles were retained for a short time in the dilated heart before being thrown out into the blood stream. Another remarkable thing is that in the first examination, when the decompensation was most pronounced, the level of activity at the first, second, fourth, and sixth hours was higher than in the earlier examinations. The figure for the twenty-fourth hour is in fact as high as that for the twentieth minute. This persistence of activity at a high level for a number of hours differs considerably from the behavior shown by normal patients. In later studies made when the decompensation was improving, the duration of activity, as shown by the graphs, changed again and approached the normal. Thus in the examination of Feb. 25, 1946 (Fig. 4), one finds that the activity after one, two, and four hours was more or less the same as after the corresponding number of minutes. The small discrepancy that does exist can be explained by the fact that the im-

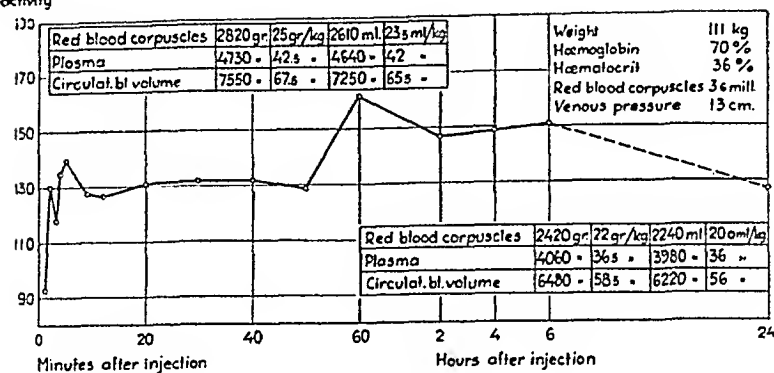
TABLE I. THE VOLUME OF RED BLOOD CORPUSCLES IN HEART FAILURE BEFORE AND AFTER COMPENSATION

Case	21						22				23				24			25		26		27
Diagnosis	Cardiosclerosis						Aortic regurgitation				Mitral stenosis				Mitral stenosis			Hypertension		Cardiosclerosis		Mitral stenosis
Date	11. 2.	25. 2.	20. 3.				14. 1.	28. 1.	6. 5.	1. 2.	18. 3.	26. 3.	9. 4.	5. 3.	14. 4.	6. 5.		27. 3.	18. 4.	11. 4.	8. 6.	8. 3.
Cell volume Grams	2,820	2,830	2,260				2,980	2,980	2,290	2,100	1,700	2,060	1,980	2,840	1,960	2,140 2,220		3,010	3,100	2,210 2,200	2,185	2,240
Grams per kilogram	30 (25)	30 (29)	24 (24)				46 (41)	46 (44)	35 (34)	35 (33.5)	28 (28)	34 (34)	33 (33)	44 (43)	30 (31)	33 (33) 34 (34)		40.5 (40)	42 (42)	26 26	26	43 (41.5)
Hematocrit	36%	40%	40%				41%	38%	35%	54%	45%	45%	48%	41%	42%	42%		53%	50%	41%	46%	51%
Plasma (Gm.)	4,730	3,850	3,340				4,055	4,600	4,020	1,830	1,970	2,380	2,030	3,850	2,550	2,780 2,890		2,530	2,930	3,000 3,000	2,495	1,960
Blood volume (Gm.)	7,550	6,680	5,600				7,035	7,580	6,310	3,930	3,670	4,440	4,010	6,690	4,510	4,920 5,110		5,540	6,030	5,210 5,200	4,680	4,200
Weight loss	1.6 kg	15.6 kg	18.6 kg				0 kg	9 kg	10 kg	1.5 kg	4.5 kg	3.5 kg	4.5 kg	—	1 kg	0 kg		8.3 kg	10.3 kg	—	—	0.7 kg
Venous pressure (Cm.)	13	8	6				27	13	16	23	10.5	11	7	12.5	16	14		10	6	17	3.5	19
Edema	+++	+	—				++++	++	+	++	—	—	—	—	—	—		++	—	+	—	++

February 11, 1946

J 92/46

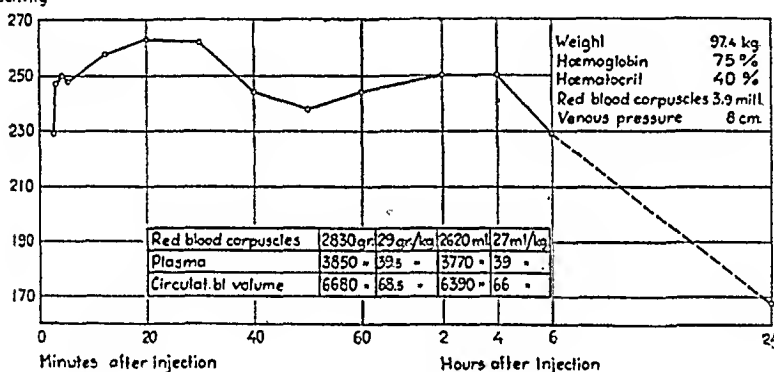
Specific activity



Case 21

February 25, 1946

Specific activity



Case 21

March 20, 1946

Specific activity

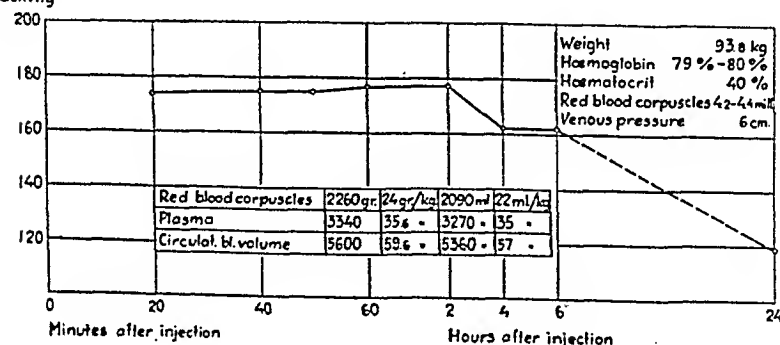


Fig. 4. — Findings in Case 21. See text.

Heart Failure

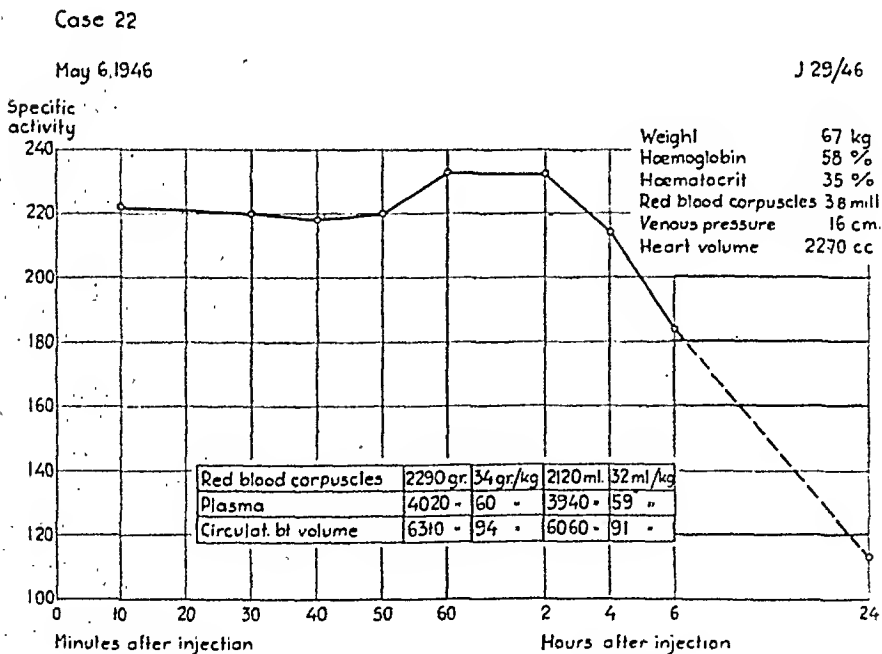
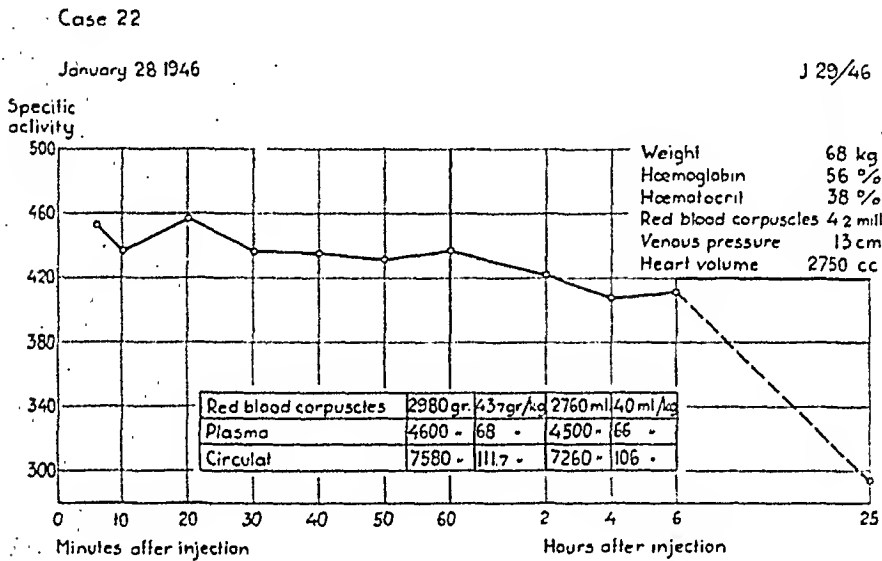
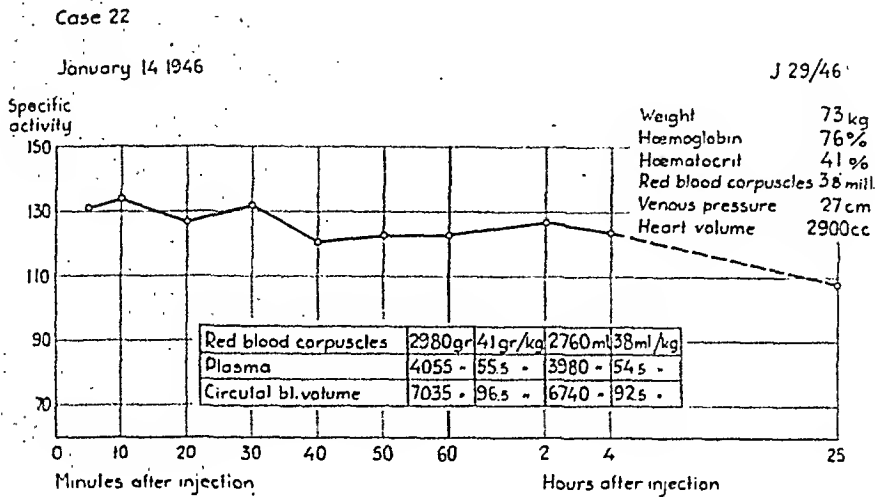


Fig. 5.—Findings in Case 22. See text.

pulses were calculated at a very high level of activity. On this occasion, the figures for the sixth, and particularly the twenty-fourth, hour signify a definite decline. After full compensation was restored, the decline in activity began after two hours. We will return in a later discussion to the interpretation of these interesting phenomena.

CASE 22.—A 68-year-old man with aortic regurgitation and a positive Wassermann had had symptoms of cardiac insufficiency for about eight years (Fig. 5 and Table I). On being admitted to the hospital, he was suffering from severe decompensation with extreme edema, severe cyanosis and dyspnea, hepatomegaly, and a venous pressure of 27 cm. of water. The volume of the heart was 2,900 cubic centimeters. Examination showed the blood corpuscular weight to be 2,980 grams, which was equivalent to 41 grams body weight or 46 per kilogram of dry weight. The plasma weight was found to be 4,055 grams and the weight of the whole blood was found to be 7,035 grams. The decompensation became progressively worse, but incision of the dorsal surfaces of the feet, as described by Nylin and Björck, and intravenous injections of cedilanid resulted in the patient's losing a considerable quantity of fluid and 9 kilograms in weight. The venous pressure was reduced to 13 cm. H_2O and the volume of the heart to 2,750 cubic centimeters. The blood corpuscular weight remained the same, 2,980 grams, but there was an unexpected increase in the plasma and whole blood, the former rising by 545 grams to 4,606 grams. The fall in the hematocrit reading from 41 to 38 per cent and in the hemoglobin from 76 to 56 per cent also indicates that the proportion of cells to plasma underwent a change in the interval between the two examinations. We have previously stressed the fallacy of judging true proportion of blood corpuscles to plasma in the whole circulation by a hematocrit reading based on blood drawn from a vein in the arm. This increase in plasma, therefore, should be treated with reserve.

About three months later, when the patient was in fairly good condition with only slight edema and cyanosis, a venous pressure of 16 cm. H_2O , and the heart volume had diminished to 2,270 c.c., we found that whole blood, plasma, and blood corpuscles had all diminished, the latter by no less than 690 grams to 2,290 grams (equivalent to 35 grams per kilogram of dry weight or 34 grams per kilogram of body weight). The change in the proportion of blood corpuscles to plasma was seen again; the hematocrit reading fell to 35 per cent, the hemoglobin to 58 per cent, and the red blood corpuscles to 3.8 million. In addition to cardiac insufficiency, anemia was present throughout the study. Variations in the anemia were presumed to be due to the change in the amount of blood corpuscles and plasma consequent upon the elimination of the decompensation. The plasma protein was fairly constant throughout at about 7.1 per cent.

The individual graphs show certain features analogous to those mentioned in the previous case. At the height of decompensation, the activity of the erythrocytes remained constant from the fortieth minute to the fourth hour; the activity at the twenty-fourth hour was again remarkably high. As the decompensation improved, there was again a fall in activity, first from the sixth hour and later from the fourth hour. This matter will be discussed later.

CASE 23.—A 32-year-old man with mitral stenosis had had symptoms of cardiac insufficiency for about four years. This patient differed from the previous patients inasmuch as the insufficiency chiefly expressed itself in pulmonary congestion with severe dyspnea and cyanosis and a palpable liver but only slight edema (Table I and Fig. 6). The venous pressure was 23 cm. H_2O , and the volume of the heart 1,750 cubic centimeters. An estimation of the blood corpuscles while the patient was in decompensation showed their weight to be 2,100 grams, equivalent to 33.5 grams per kilogram of body weight or 35 grams per kilogram of dry weight. The whole blood amounts to 3,930 grams and the plasma to 1,830 grams. After compensation, with a fall in the venous pressure to about 10 cm. H_2O and in the volume of the heart to 1,460 c.c., the blood corpuscular weight was found to have remained fairly constant, the figures being 1,700 grams on March 17, 2,060 grams on March 23, and 1,980 grams on April 9, 1946. These figures are equivalent to 28, 34, and 33 grams, respectively, per kilogram of dry weight. The whole blood also remained fairly level, the figures being 3,670, 4,440, and 4,010 grams, respectively.

Case 23

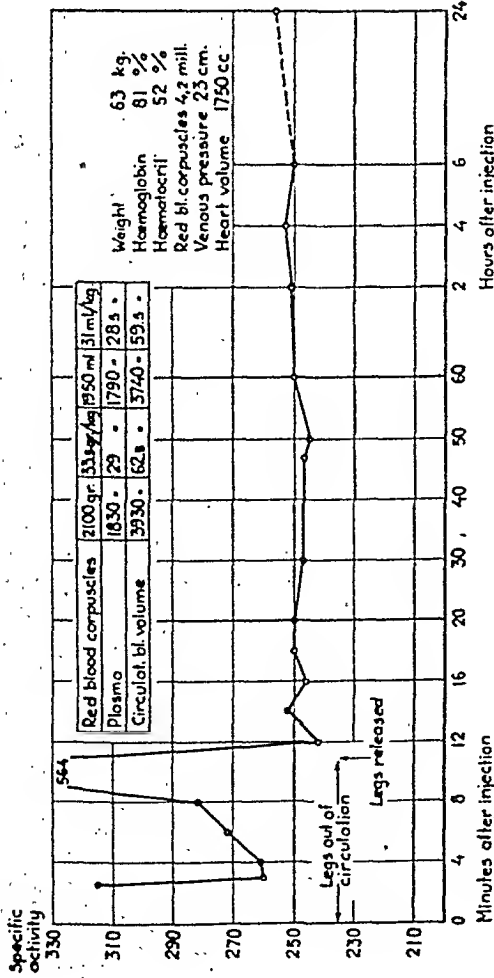
March 26 1946

Heart Failure

Case 23

February 1, 1946

J. 65/46



Case 23

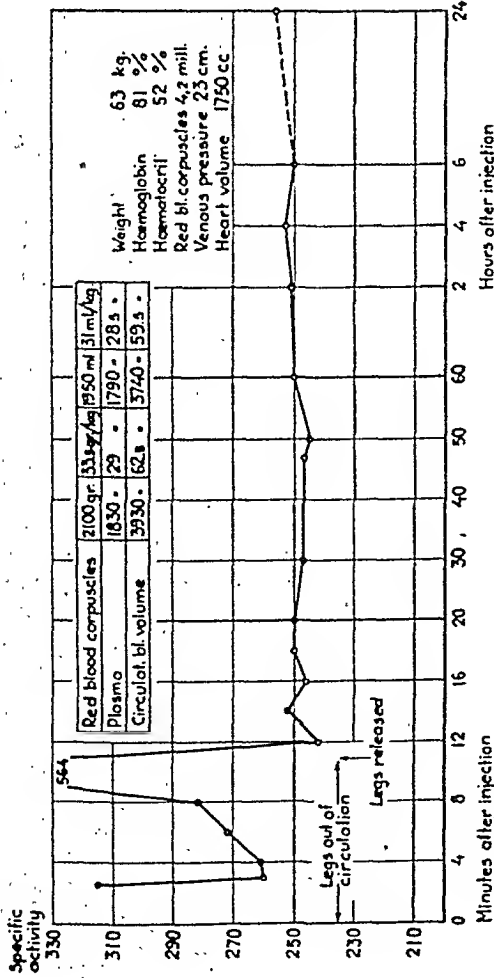
March 26 1946

Heart Failure

Case 23

February 1, 1946

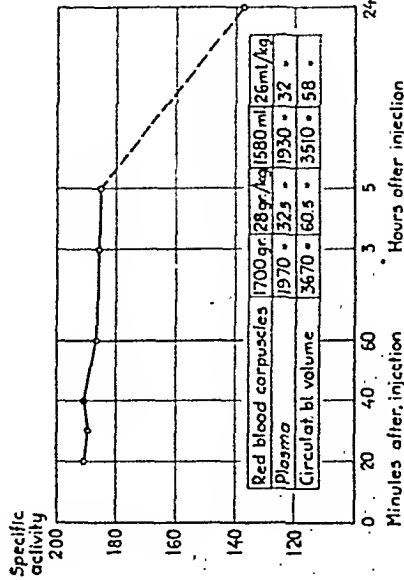
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Case 23

March 17, 1946

J. 65/46



Case 23

March 17, 1946

J. 65/46

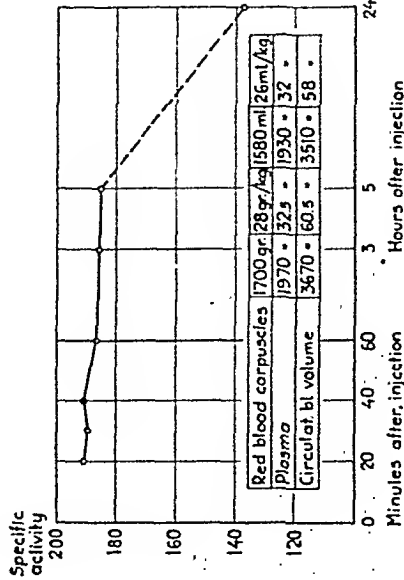


Fig. 6.—Findings in Case 23. See text.

During the examination on Feb. 1, 1946, the lower limbs were occluded for about ten minutes by cuffs applied to the upper part of the thighs and pumped up to a pressure above the systolic pressure. The cuffs were then removed; the activity figures in the later part of the graph, therefore, represent the total volume of circulating blood. In this manner, one can determine the amount of blood in the lower limbs. We will not discuss this matter on this occasion because it will be presented in another paper, but it is worthy of note that in this experiment a considerable number of impulses were recorded just before the cuffs were taken off. This is not easy to explain. A possible explanation is that some of the labelled corpuscles may have been delayed in the dilated heart or in some other organ where the circulation rate is reduced (the liver, for example), and may have been prevented from promptly reaching the faster circulation from which the blood samples were taken. This case also shows that during decompensation the activity of the labelled corpuscles remains constant up to the twenty-fourth hour after injection. After compensation has been established, there is again a steady fall in activity from the fifth hour, and in the final examination from the third hour.

CASE 24.—The patient was a 35-year-old man suffering from mitral stenosis who had had symptoms of cardiac insufficiency for about eight years (Table I and Fig. 7). As in the previous case, the decompensation showed itself in pulmonary congestion with severe dyspnea and a palpable liver, but no edema. The venous pressure fluctuated throughout between 12.5 and 16 centimeters. In the first examination, the corpuscular weight was found to be 2,840 grams, which was equivalent to 44 grams per kilogram of dry weight or 43 grams per kilogram of body weight. The whole blood weighed 6,690 grams and the plasma 3,850 grams. A month later, after treatment with digitalis, the corpuscular weight had fallen to 1,960 grams or 31 grams per kilogram of body weight. The plasma had diminished to 2,550 grams, and the whole blood to 4,510 grams. The reduction in corpuscular weight was, therefore, 880 grams, or 12 grams per kilogram of body weight. After another month had elapsed, the corpuscular weight was found to be practically unchanged; that is, 2,140 and 2,220 grams, respectively, as determined by double injection. The corresponding figures per kilogram of body weight were 33 and 34 grams, respectively. Figures for whole blood were 4,920 and 5,110 grams, respectively. The hematocrit reading was the same throughout, showing that the proportion of blood corpuscles to plasma was constant. The hemoglobin, on the other hand, fell from 80 per cent in the first examination (during decompensation) to 74 per cent in the second and 75 per cent in the third examination.

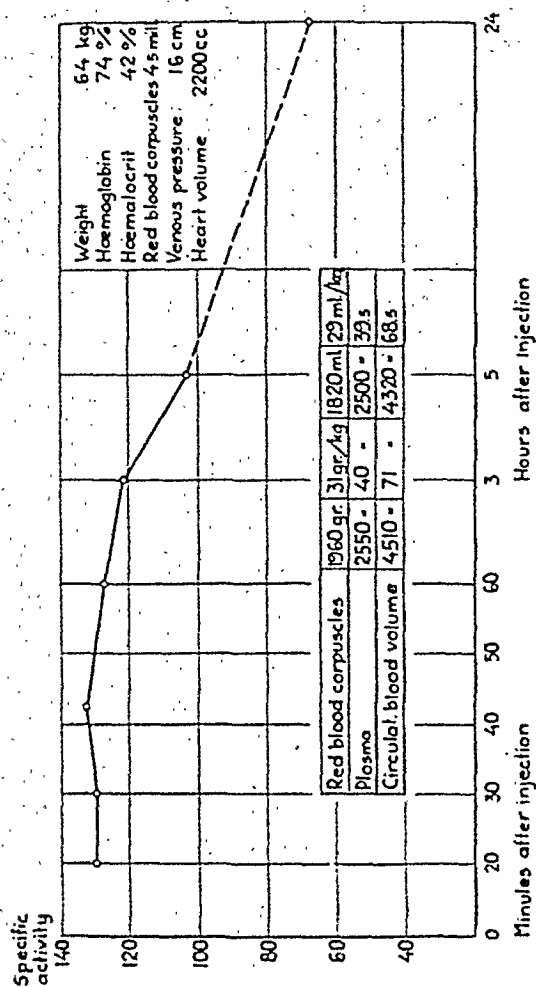
In the first examination of this case, we made a slight change in the usual routine; the blood samples were obtained by arterial puncture. This gives a dilution graph which shows the progressive mixing of the labelled corpuscles with the blood. As has already been mentioned, cardiac insufficiency causes a change in the appearance of this graph by displacing it to the right in a characteristic manner. In this case, the maximum activity was not reached until the fortieth to forty-fifth second, and equilibrium was not established until the ninth minute. At the sixth minute, the patient moved the arm into which the labelled corpuscles were injected, and the blood samples taken during the subsequent two minutes displayed a considerably increased activity. It is probable that this peak is due to labelled corpuscles having remained at the site of the injection until the active movement of the arm released them into the blood stream.

Heart Failure

Case 24

April 14, 1946

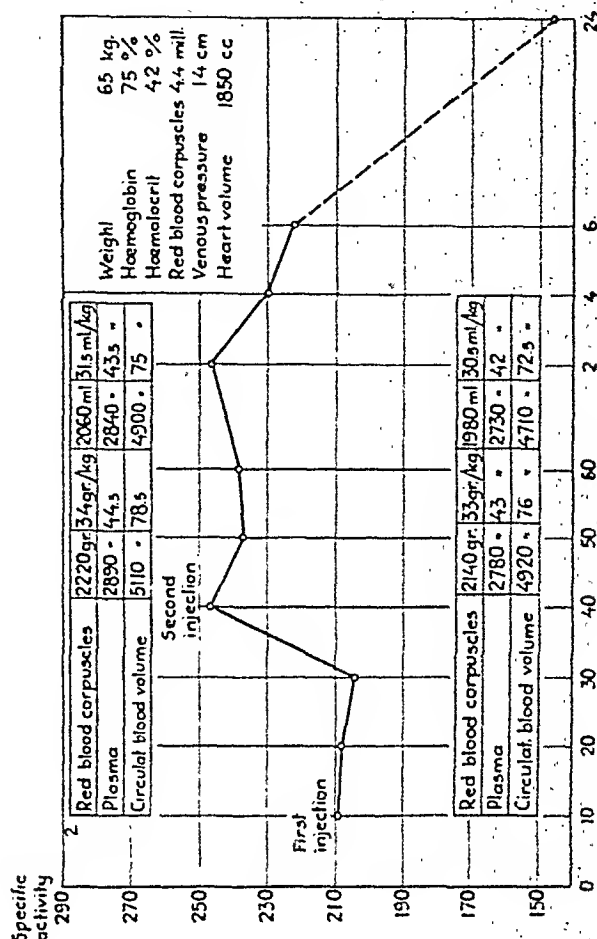
J 224/46



Case 24

May 6, 1946

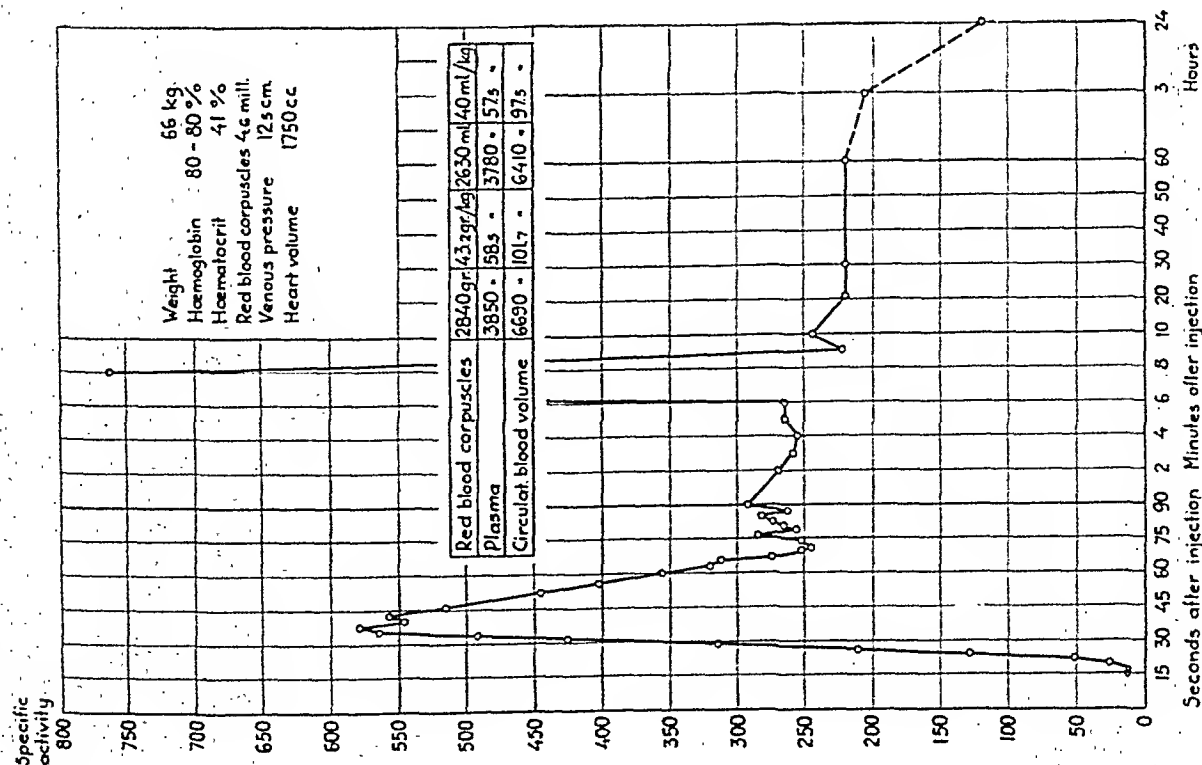
J 224/46



Case 24

March 5, 1946

J 224/46



cm. H₂O, the corpuscular weight was found to be 3,010 grams, or 40 grams per kilogram of body weight; the plasma weight 2,530 grams; and the whole blood 5,540 grams. Three weeks later after complete compensation had been restored, and the venous pressure has fallen to 6 cm. and the volume of the heart to 1,300 c. c., another determination showed the weight of the corpuscles to be unchanged: 3,100 grams or 42 grams per kilogram of body weight. Thus there had been no diminution in the quantity of blood corpuscles, which was still large. The whole blood weighed 6,030 grams and the plasma 2,930 grams. Although there had been a further reduction in the edema (about 2 kilograms), there had been, if anything, an increase in plasma. The explanation is perhaps to be sought in the fact that the serum protein had risen from 5.8 per cent in the first examination to 7.2 per cent in the second examination. In addition to the pressure of extracellular fluid, the plasma proteins constitute an important factor in the maintenance of plasma volume. In this case, the hematocrit readings, 53 per cent and 50 per cent, respectively, the hemoglobin, 87 per cent, and the count of red blood corpuscles, 5.1 million, also indicate that there had been an increase in the total quantity of erythrocytes. Fig. 8 shows the graphs based on these two examinations.

CASE 26.—A 50-year-old man suffering from cardiosclerosis had had symptoms of insufficiency, mainly in the form of unpleasant breathlessness, for about one year (Table I and Fig. 9). Examination showed his principal symptoms of decompensation to be dyspnea, cyanosis, and slight edema at the ankles. The venous pressure was 17 cm. H₂O and the heart volume 1,850 cubic centimeters. In the first examination, while there was decompensation, double injections of labelled corpuscles showed the corpuscular weight to be 2,210 and 2,200 grams, respectively, equivalent to 26 grams per kilogram of body weight. Thus, the difference in this estimation was only 10 grams. After being treated for two months, compensation was restored; the volume of the heart had declined to 1,080 c.c. (later the volume declined to 800 c.c.), and the venous pressure had declined to 3.5 cm. of water. Another determination of corpuscular weight by double injections showed it to be unchanged, the figures on this occasion being 2,290 and 2,080 grams, respectively, a difference of only 200 grams. These figures correspond to 27 and 25 grams per kilogram of body weight, respectively. While there was decompensation, the whole blood measured 5,200 grams and the plasma 3,000 grams. After compensation had been restored, the plasma value declined to 2,500 grams, and the whole blood value declined to about 4,700 grams. The rise in the hematocrit reading from 41 to 46 per cent and in the hemoglobin from 56 to 81 per cent also indicated that there has been an increase in the proportion of blood corpuscles to plasma. Fig. 9 shows the graphs of the double injections on both occasions.

CASE 27.—A 42-year-old woman had had symptoms of insufficiency for ten to fifteen years. On admission to the hospital, her most obvious symptoms were dyspnea and cyanosis. She had a palpable liver, only slight edema, a venous pressure of 19 cm. H₂O and a heart volume of 1,980 cubic centimeters. The corpuscular weight, determined in this decompensation phase, was found to be 2,240 grams or 43 grams per kilogram of dry body weight. The whole blood measured 4,200 grams and the plasma 1,960 grams. The hematocrit reading, 51 per cent, also suggested an abnormally high proportion of erythrocytes (Table I and Fig. 10).

Fig. 10 shows that equilibrium was established late (not until the fiftieth minute), but that the activity remained constant up to the sixth hour after injection. Without doubt the labelled blood corpuscles were delayed in organs where the circulation was slow and in the dilated heart and did not reach the faster circulation and mix completely with the rest of the blood promptly.

DISCUSSION

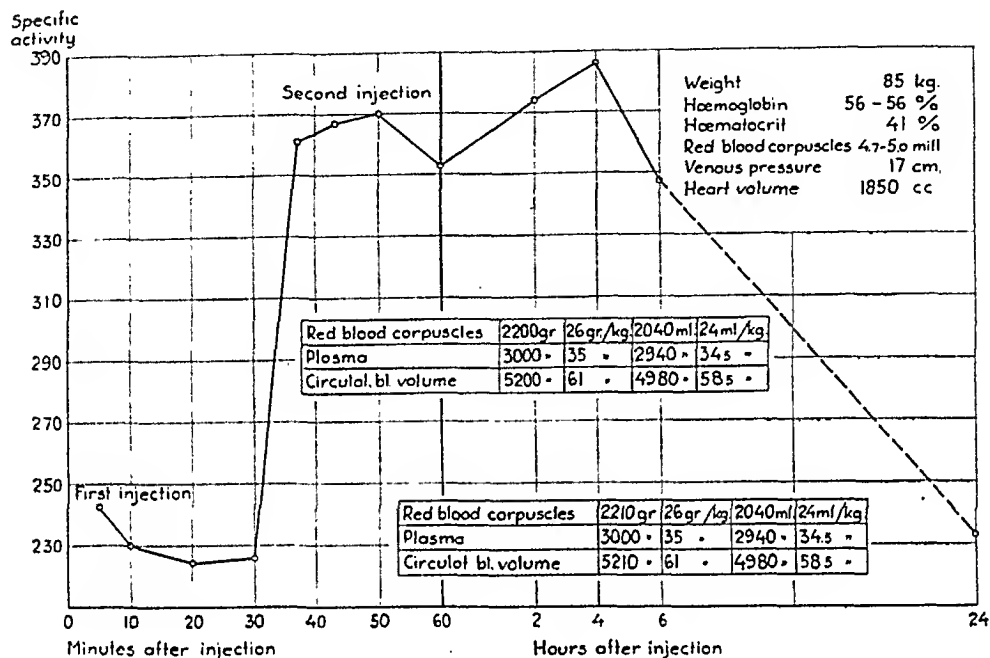
A comparison between the corpuscular weight (in grams per kilogram of dry body weight) in normal patients and in patients with heart disease during compensation and decompensation is shown in the form of a graph in Fig. 11.

Case 26

Heart Failure

April 11, 1946

J. priv.



Case 26

Heart Failure

June 8 1946

J. priv.

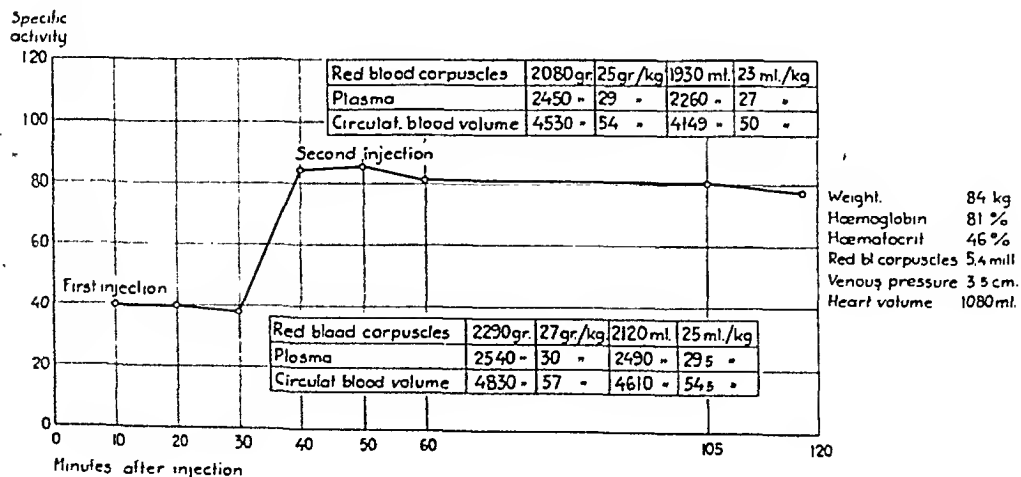


Fig. 9.—Findings in Case 26. See text.

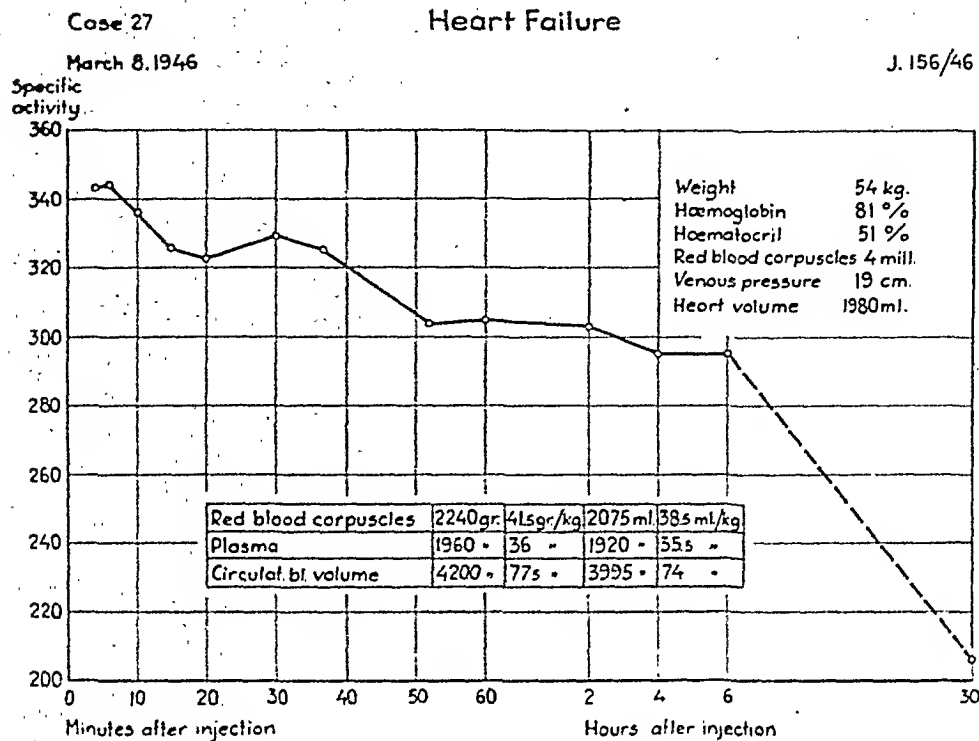


Fig. 10.—Findings in Case 27. See text.

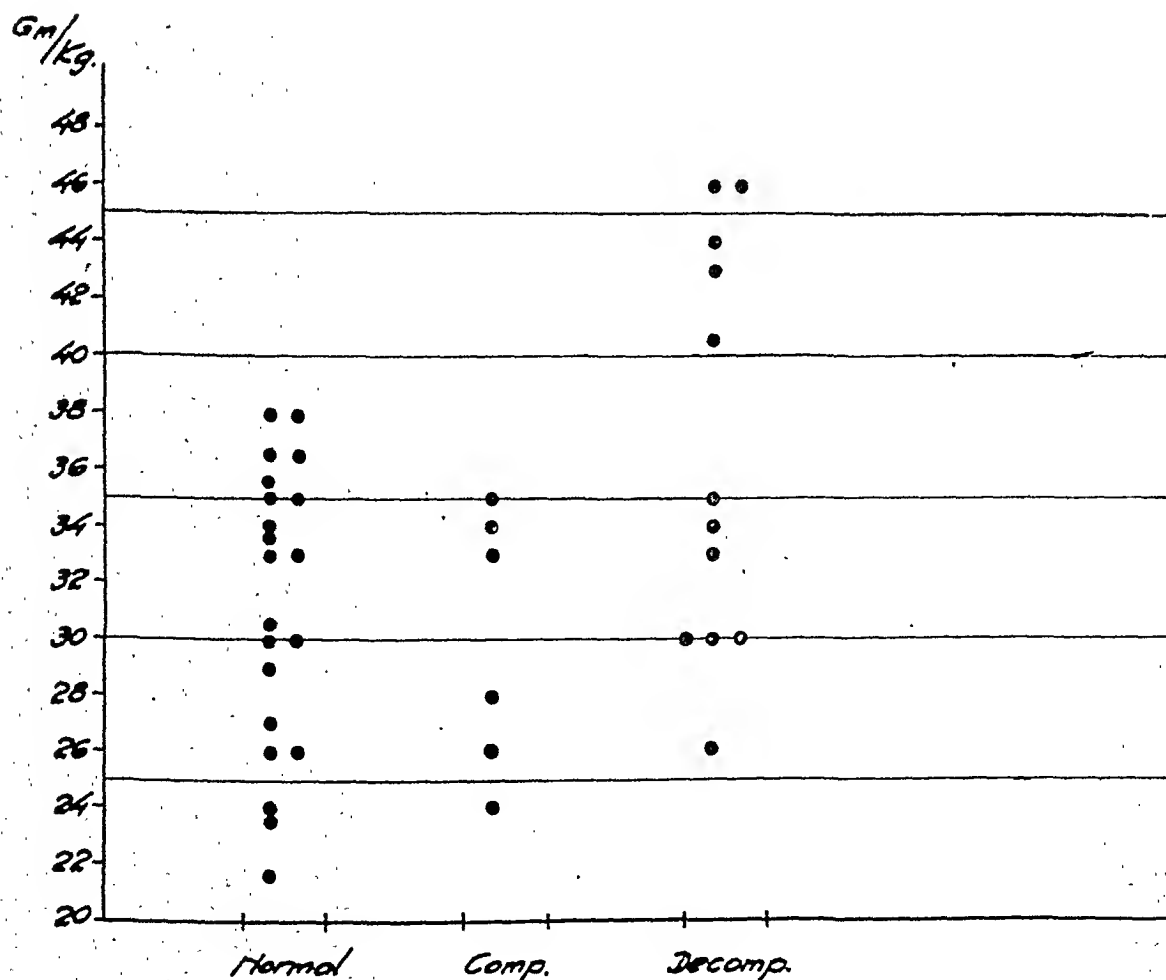


Fig. 11.—Comparison of weight of corpuscles (in grams per kilogram of dry body weight) in normal subjects with the weight of those in patients with heart disease during the stages of decompensation and compensation.

The average corpuscular weight in normal individuals, as previously mentioned, is 31.2 grams $\pm 3 \times 1.06$. The range in these normal cases is from 21.5 to 38 grams. The average weight of the corpuscles in decompensated patients, on the other hand, is 36.4 grams per kilogram $\pm 3 \times 1.94$. The range in this group is from 26 to 46 grams. The increase in corpuscular weight in decompensation is thus statistically demonstrated. The range in the small number of compensated cardiac patients appears to correspond more or less to the normal. It is thus seen that the corpuscular weight per kilogram of dry body weight in patients with cardiac insufficiency falls, after compensation has occurred, to the level observed in normal patients. In some cases, restoration of compensation was not only accompanied by a reduction in the amount of whole blood and plasma, indicating a loss of fluid, but also by a reduction in the total number of erythrocytes. In most cases, decompensation was accompanied by an increase in the amount of whole blood and of erythrocytes. It appears that the increase in whole blood, which is a feature of decompensation, is particularly pronounced in patients with severe edema, whereas, if the decompensation expresses itself mainly in pulmonary congestion, and peripheral edema is insignificant, then there is only a slight increase in the number of red corpuscles. With the material at our disposal, we cannot yet draw any definite conclusions as to a correlation between the duration of insufficiency symptoms and the total number of red blood corpuscles. It is not improbable, however, that a significant increase in the number of erythrocytes actually occurs in patients who have suffered from insufficiency for many years.

It is also clear from the investigation that an abnormally high venous pressure must not be regarded as a sign of excess blood. It is precisely in those cases where pulmonary stasis is the only or the primary sign of decompensation and the venous pressure is abnormally high that one finds the volume of blood to be practically normal. The venous pressure does not, therefore, determine the volume of the blood nor is the latter the sole factor regulating the venous pressure. In cases with both excessive blood volume and high venous pressure, there is a reduction in both during recovery. Meneeley and Kaltreider⁴³ and others have also drawn attention to this absence of correlation between venous pressure and blood volume.

We have already remarked upon certain curious features of the various graphs which show the specific activity of the erythrocytes at different times during decompensation and compensation. Thus, one cannot fail to notice that in decompensation the activity remains constant for a remarkably long time: for four, six, or even twenty-four hours after injection. In certain cases activity actually increases for these long periods of time. After compensation has been restored, the appearance of the graphs undergoes a gradual change; the fall in activity sets in earlier and finally the graph appears more or less normal. Case 21 illustrates these changes very well.

Fig. 12 shows in the form of a graph the fall in the activity of the erythrocytes over a period of twenty-four hours in normal subjects and in decompensated patients. Each plotted point represents the average for a number of measurements. The time values are expressed as percentages of the specific activity of

the equilibrium value. The graphs show that the fall in activity almost corresponds to a straight line and that it commences earlier and proceeds more rapidly in normal cases than in those where decompensation is present. The same is true of the activity of the plasma; Fig. 13 shows in graph form the fall in plasma activity expressed in percentages of the specific activity at the tenth minute. A conceivable explanation of these phenomena is that in cases of cardiac insufficiency the activated blood is retained somewhere in the body, possibly in some congested region such as the portal system and liver, and delayed in reach-

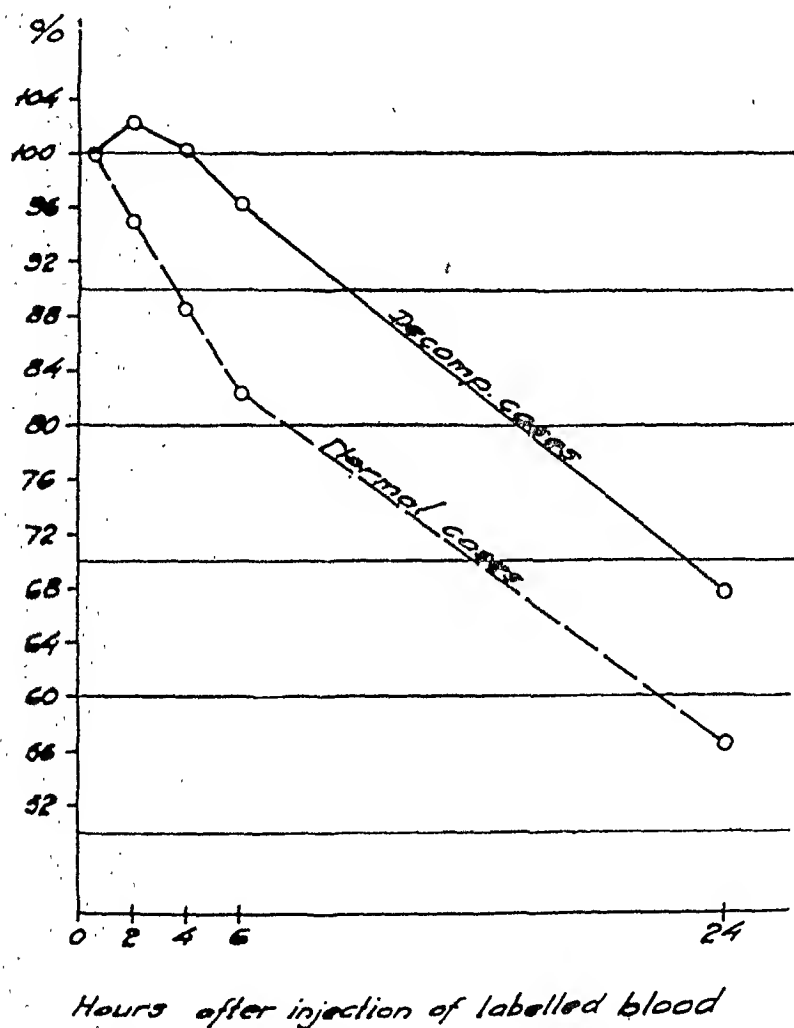


Fig. 12.—The fall in the activity of the erythrocytes during a period of twenty-four hours in normal subjects and in patients with decompensation.

ing the faster circulation from which the venous samples are taken. When compensation occurs, the portal stasis is eliminated, the circulation is accelerated, and the blood corpuscles reach the arm vein sooner. The result is that the decline in activity of blood corpuscles and plasma resembles that seen in normal persons. It is also possible that the permeability of the corpuscular membrane to the phosphate ion P^{32} may be different in the normal and decompensated circulations and that this may affect the activity. Thus, a blood corpuscle with a high resistance in decompensation might less easily give up its phosphate ions once it has been activated.

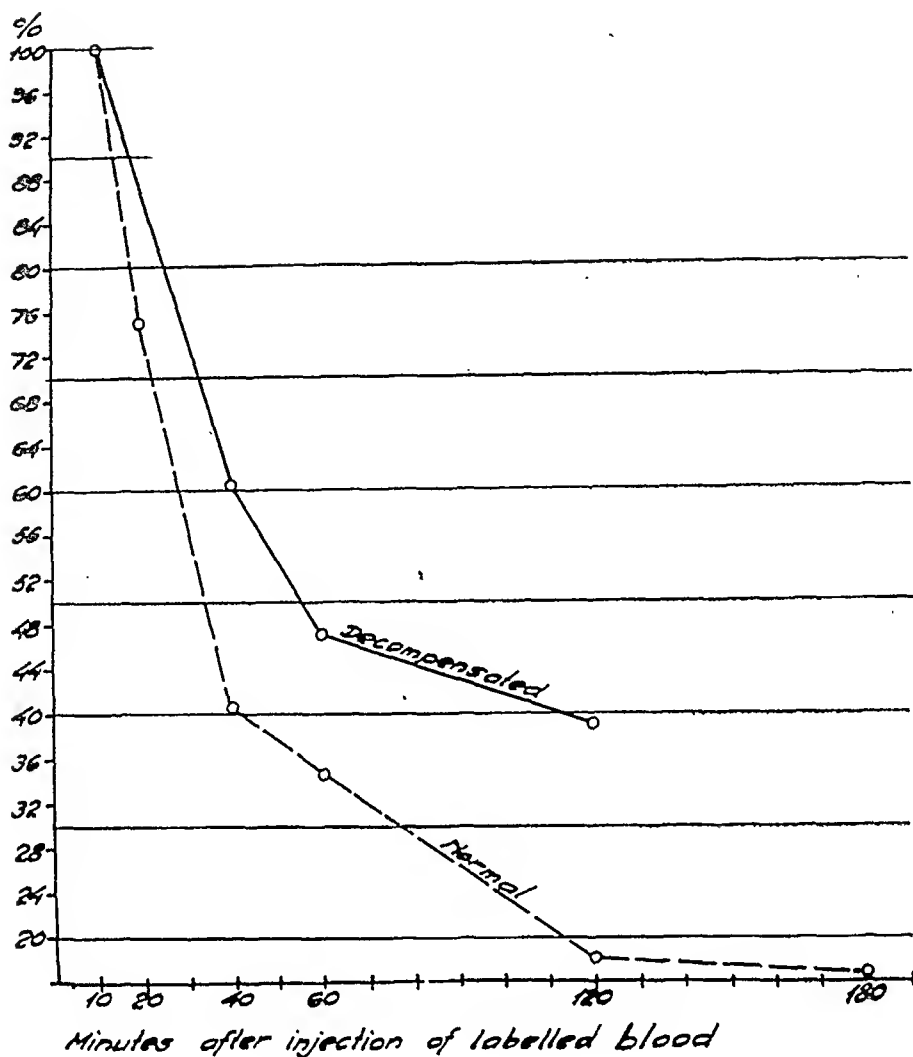


Fig. 13.—The fall in the activity of the plasma during a period of twenty-four hours in normal subjects and in patients with decompensation. The fall in activity is expressed in percentages of the specific activity at the tenth minute after injection.

SUMMARY

1. The different methods of estimating blood volume are reviewed. The inherent faults of the blue azo dye method for estimating plasma volume are stressed. Since the concentration of this substance constantly diminishes in the circulating blood, the point at which equilibrium (balance) is established is difficult to determine accurately. Even in the carbon monoxide method there is no considerable period when there is a constant amount of the test substance in the circulating blood, since a quantity, difficult to measure, is absorbed by the myoglobin. The introduction of Hevesy's method for labelling the blood corpuscles with radioactive phosphorus, however, has contributed greatly to the study of different problems of circulation. One of the advantages of this method lies in the fact that the test substance maintains a constant activity in the blood for as long as an hour. Certain opinions and conclusions that have come from

experience with this method are discussed. The use of the hematocrit for estimating the blood volume is also discussed.

2. A variation of the original method which employs radioactivated whole blood (both corpuscles and plasma) is described. The blood corpuscles maintain their activity up to sixty minutes, while the activity of plasma falls to one-tenth of its original value after five minutes.

3. By the use of this procedure the quantity of blood corpuscles was estimated in seven cardiac patients both in the stage of decompensation and after compensation had been restored. In decompensated cardiac patients there is not only an increase in the total quantity of blood and plasma, but also in the amount of erythrocytes. After compensation is restored, both the plasma and blood corpuscles decrease in quantity. There is a clear difference in the quantity of blood corpuscles, measured in grams per kilogram of dry body weight (the weight of the body when there is no edema), in decompensated patients and in normal subjects. In decompensated patients the quantity of erythrocytes is, on the average, 36.4 grams per kilogram of dry body weight; in normal subjects, this value is 31.2 grams per kilogram of dry body weight. About the same quantity of erythrocytes is found in compensated cardiac patients as is found in normal subjects. In normal subjects there is a correlation between the total quantity of blood corpuscles and the body weight.

4. The importance of a knowledge of the form of the dilution curve for the labelled blood corpuscles is stressed. Estimation of the circulation time by this method in cardiac patients with dilated hearts, but no peripheral edema, supports the view that blood is retained in dilated hearts and that this factor greatly influences the estimation of the circulation time. A comparison between the dilution curves in decompensated patients and normal subjects shows that the activity is reduced slowly in decompensated patients. This seems to indicate that the activated blood is kept for a certain time within the congested area.

We wish to express our sincere thanks to the Swedish Board of Medical Research, the financial assistance of which has enabled us to carry out these investigations.

We present our compliments to Prof. G. de Hevesy, who has constantly shown an interest in our studies. We are likewise grateful to Prof. M. Siegbahn, who procured radioactive phosphorus for our work.

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ELECTROCARDIOGRAMS WITH LARGE, UPRIGHT T WAVES AND LONG Q-T INTERVALS

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ELECTROCARDIOGRAMS with rather large, upright T waves are not very unusual. Among adults, they are most often seen in sinus bradycardia, and usually in association with R waves of average or greater than average amplitude. In healthy persons whose electrocardiograms are of this type it has been suggested that the spatial ventricular gradient is parallel to the frontal plane, and the magnitude of the gradient is large because of the bradycardia.¹

In a later statistical study, the mean magnitude of the ventricular gradient* of eighty men was estimated at 11.77 ± 0.39 units of 4 microvolt-seconds each, each unit being equal to a single small rectangle on the film with usual standardization and timing.² The standard deviation was 4.52 ± 0.24 units. Hence, the normal range in magnitude of the gradient appeared to be from -1.8 to $+25.3$ units. This indicates that about one normal person in 370 will have a gradient outside this range. In a group of eighty-four women, G (the magnitude of the gradient) averaged 11.34 ± 0.27 units, the standard deviation was 3.67 ± 0.19 units, and the range at 3 standard deviations was $+0.3$ to $+22.3$ units of area. These figures have the value that they enable us to say that in certain cases the gradient and the T waves are unusually or abnormally large.

The electrocardiogram shown in Fig. 1 was taken on April 8, 1938, on a 47-year-old ambulatory Negro woman who complained of substernal "heaviness," occasional sharp pains over the precordium, and palpitation on exertion. At that time arterial blood pressure was 270/158 and the Wassermann was negative.

No record is available for the period between April, 1938, and December, 1939. At this later date on the occasion of a visit to a friend's house the patient was seized with a "smothering" feeling and ascending numbness of the left lower extremity. She attempted to walk home, but the symptoms became more severe and the smothering feeling changed to severe substernal pain with radiation down the left arm. This was shortly followed by a period of unconsciousness during which time she had several convulsions and vomited. Consciousness returned spontaneously in a few minutes. On his arrival, an ambulance physician noted cyanosis and profuse sweating. A small white pill placed under the patient's tongue brought relief from the substernal pain. She was placed at bed rest.

On Jan. 2, 1940, a physician was consulted for the precordial pain, and at this time the patient was hospitalized. Physical examination revealed an arterial blood pressure of 242/160, a heart

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*The ventricular gradient of Wilson is the manifest mean area of the whole ventricular complex, QRS-T.

rate of 75 beats per minute with a regular rhythm, and marked cardiac enlargement. The aortic second sound was accentuated. Neurological examination was reported as showing no abnormalities. The diagnosis was recorded as "hypertensive cardiovascular disease, coronary occlusion versus angina pectoris, and possible hypertensive encephalopathy." She left the hospital in about three weeks.

On Dec. 2, 1940, the patient was again admitted to the hospital following a "falling out" attack at home. She was conscious but semistuporous on admission and complained of severe right frontal headache. On physical examination the arterial blood pressure was 235/130. The only neurological finding was weakness of the left hand. A spinal tap revealed a spinal fluid pressure of 300 mm. of water and a grossly bloody fluid with a clear supernatant portion on centrifugation.

On December 3, the patient had meningismus with positive Brudzinski and Kernig signs. Left hemiparesis was present.

On December 4, the electrocardiogram shown in Fig. 2 was taken. The blood urea nitrogen on this date was 78/4 mg. per cent.

On December 6, the spinal fluid was xanthochromic and under pressure of 150 mm. of water. By December 9, the urea nitrogen was 14 mg. per cent and the patient's neurological signs were diminishing.

On Aug. 8, 1943, the patient was sent in from the clinic for another electrocardiogram with the complaint of "pain over her heart, smothering spells, and weakness." Arterial blood pressure at this time was 180/105. At no time throughout this period had she received digitalis, nor were there signs of congestive failure.

Electrocardiographic Findings.—The electrocardiogram of Fig. 1, taken in 1938, is not unusual. The mean heart rate is 63 per minute, the P-R interval is 0.145 to 0.165 second, the duration of the QRS complex is 0.09 second or

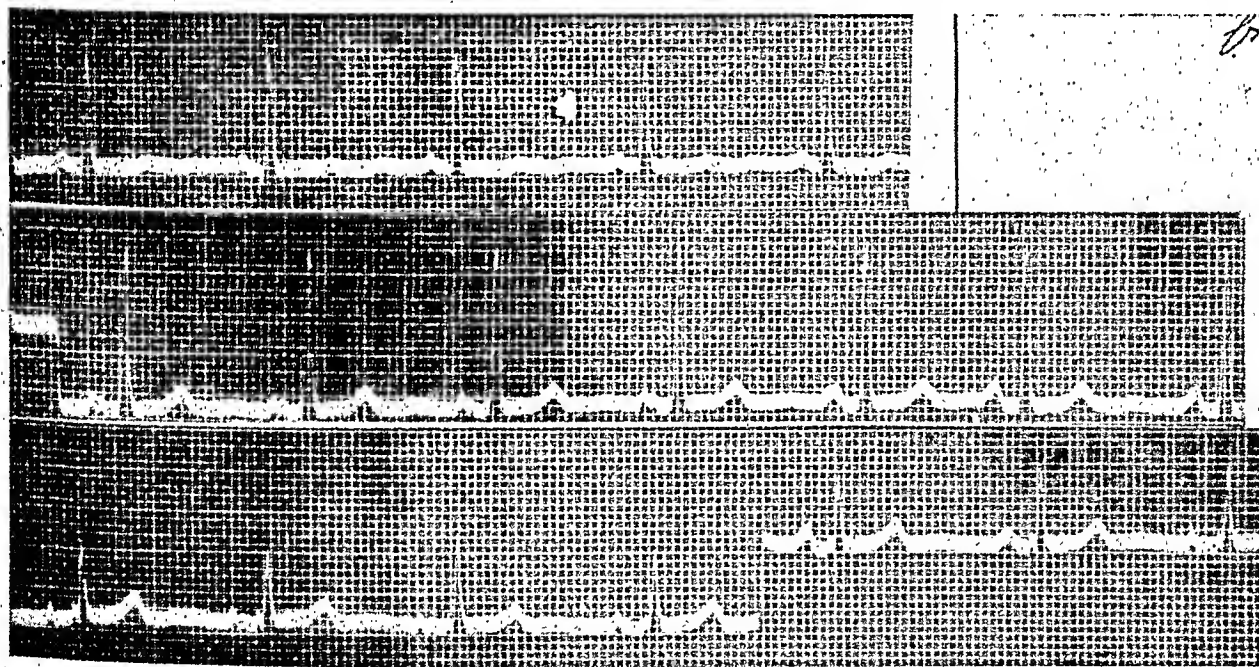


Fig. 1.—Electrocardiogram taken April 8, 1938. The low T wave in Lead I is partly primary and partly secondary.¹¹ On Jan. 20, 1940, another electrocardiogram was like this one, except for lower T waves in all limb leads; the heart rate was practically the same.

slightly more, and the Q-T interval is 0.41 second, which puts it near the upper limit of the normal. The magnitude of A_{QRS} is 14.0 units (56.0 microvolt-seconds) and, therefore, large,¹ suggesting hypertrophy of the left ventricle. The T wave is low in Lead I and upright in Lead III; in the presence of this QRS pattern,

this is abnormal. There is a shift of pacemaker shown by the change in form of the P waves. No precordial leads were taken.

On Jan. 20, 1940, another electrocardiogram was taken. It revealed only minor changes from Fig. 1, mainly a decrease in height of T_2 and T_3 . The Q-T interval was unchanged. The precordial lead (CF₄) was like that of Fig. 2, the T waves being upright.

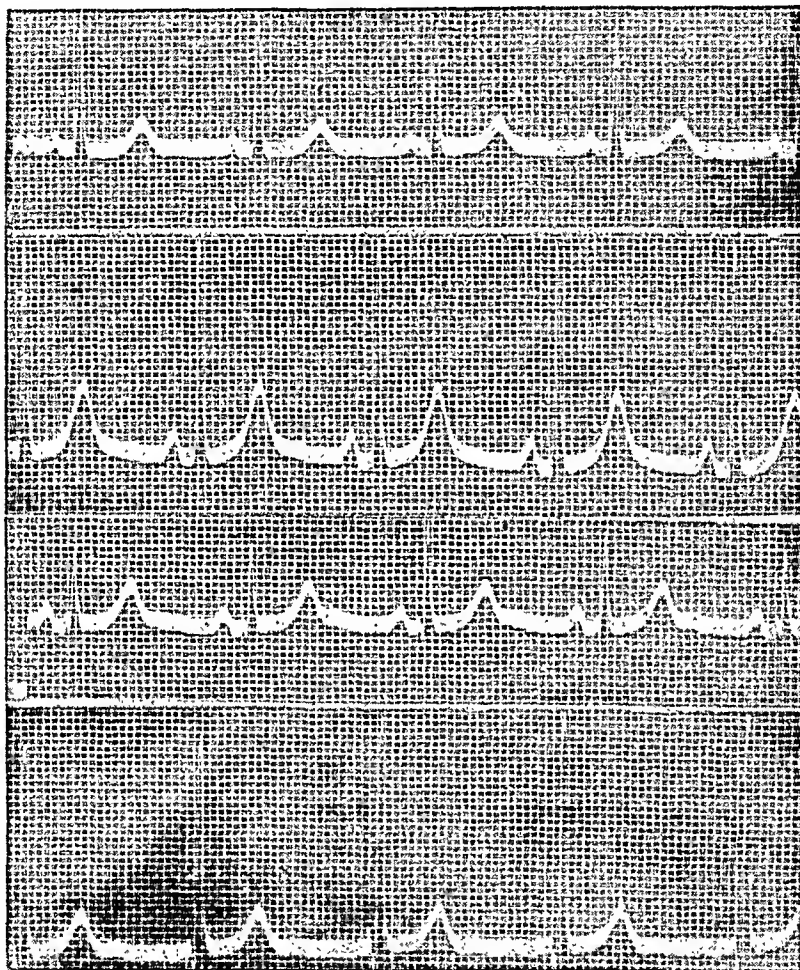


Fig. 2.—Electrocardiogram taken two days after admission to hospital in a semistuporous state in December, 1940.

The electrocardiogram of Fig. 2 was taken on Dec. 4, 1940, two days after the cerebrovascular accident. The rate is still about 63 per minute. The P-R interval is 0.16 second; the QRS duration is about 0.10 second; the Q-T interval, measured in Lead I, is fully 0.49 second. In Leads II and III, the end of the T wave is indefinite and blends with the U waves. R_1 and R_2 are larger than before. A_{QRS} is now nearly 17.0 units. The T waves are large and wide. The ventricular gradient is little changed in direction since 1938, but its magnitude has gone up from not quite 19.0 units to nearly 43.0 units.

On Dec. 13, 1940, the electrocardiogram of Fig. 3 was taken. The QRS complexes are essentially unchanged, but the large T waves have disappeared,

and the T waves are all low. The Q-T interval is again 0.40 second, the heart rate now being 75 per minute. As in Fig. 2, the P waves are higher than in Fig. 1; but the shift in pacemaker in Fig. 1 suggests that such a shift is the main reason for this increase.

The limb leads of the electrocardiogram of Aug. 8, 1943, were very similar to Fig. 1; but the R waves were larger, as in Fig. 3, and the Q-T interval in CF₄ was 0.45 second, the T wave being slightly deeper than in Fig. 3. The heart rate was 65 per minute.

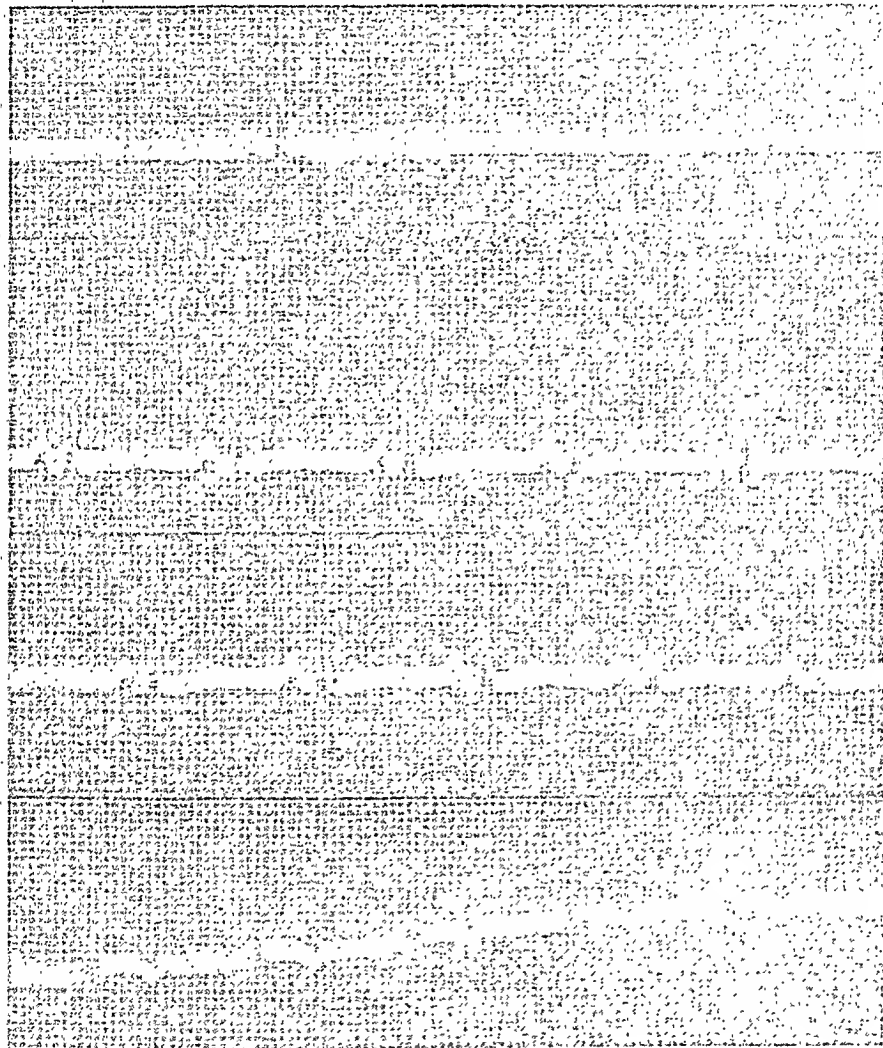


Fig. 3.—Electrocardiogram of Dec. 13, 1940, nine days after that of Fig. 2.

The striking change in this series of electrocardiograms is the increase in the height of the T waves which was recorded on the second day after the cerebrovascular accident, and the prolongation of the Q-T interval from a duration near the upper limit of the normal to 0.49 second, which is 0.08 above the upper limit.³ These changes had disappeared nine days later.

Just how large the gradient is in Fig. 3 is best demonstrated by statistical methods. If we take the average G for women to be 11.34 units, as stated in the introduction, the G in this case exceeds the average by over 31 units. If we take 4.0 units as the standard deviation, then the gradient in this case exceeds the

average by nearly 8 standard deviations. This is very far outside the normal range of gradient magnitude.

Without searching our complete files, we have found the electrocardiograms from five other cases in which large, upright T waves appeared; in two of the patients cerebrovascular accidents had occurred, while one patient had severe hypertensive encephalopathy. The changes in these patients were not so extreme as in the case described in detail.

The first of these five patients was a Negro woman, 47 years of age, whose arterial pressure was 218/148, and who had a "falling out spell," with loss of consciousness for several hours, on March 2, 1941. The first electrocardiogram, taken on March 7, indicated left ventricular hypertrophy. The T waves were low, T_1 being slightly inverted. A sharply inverted T wave in the precordial lead (CF_4) suggested ischemia of the subjacent heart wall. This patient subsequently had severe attacks of vertigo, headaches, and weakness, but there is no record of abnormal neurological findings. A second electrocardiogram, taken on August 15 of the same year, was unchanged except that T_1 , T_2 , and T_4 were rather high, and the Q-T interval was moderately prolonged. On July 27, 1942, the patient had a cerebrovascular accident with sudden loss of consciousness, followed by rapid onset of acute pulmonary edema. The arterial pressure was 220/185 at this time. The patient died within a few hours. No electrocardiogram was obtained.

The second patient was a Negro woman, 28 years old. She was admitted to the hospital on May 4, 1943, with aphasia, and was one month post partum. The pregnancy and delivery had apparently been normal. On admission the arterial pressure was 148/100. The rest of the physical examination was not contributory. Her arterial pressure in 1941 and 1945 was consistently well within the normal range. The electrocardiogram, taken on May 4, 1943, is shown in Fig. 4. The QRS complexes are within the normal range. The Q-T interval is prolonged moderately. Her gradient, at 24.4 units, is not absolutely very large, but it is large at a heart rate of 80 to 85 per minute (in Leads I and III) and with an A_{QRS} of 4.6 units. It lies at nearly 4 standard deviations from the mean.

The third patient was also a Negro woman, 49 years of age. Arterial blood pressure on admission to the hospital was 180/80. A cerebrovascular accident occurred at 6:30 P. M., Aug. 14, 1946, and the first electrocardiogram was taken on Aug. 16, 1946. The gradient was not absolutely large, because of a slight depression of the RS-T segments in Leads I and II. The diagnosis was "cerebral hemorrhage with left hemiplegia." The spinal fluid was grossly bloody, and the pressure was 200 mm. of water.

A fourth patient was a 29-year-old white woman, who, on July 1, 1941, had a normal electrocardiogram, and arterial hypertension. The electrocardiogram at that time was within normal limits, and the T waves were not high. Two months later, the blood pressure was 240/150, and the T waves in Leads I and II were large. Two years later, when the arterial pressure was reported to be 260/170, T_1 had become isoelectric (a primary change) and T_2 high. The QRS changes suggested hypertrophy of the left ventricle. Shortly afterward the patient died. The final diagnosis was "malignant hypertension."

The fifth patient was a 59-year-old white woman, whose blood pressure was 210/110. No other relevant findings are available.

Finally, we have found one apparently normal electrocardiogram from a 32-year-old Negro man. The clinical diagnosis was syphilitic aortitis. His complaints were dyspnea, substernal pain, and "weak spells." The arterial pressure was 116/78 to 110/70. The electrocardiogram shows normal QRS complexes, T waves of quite normal appearance, though rather high and wide, and a Q-T interval which is just over the upper "normal" limit. The gradient is 29.5 units, and lies at 3.9 standard deviations from the mean. An earlier electrocardiogram on this patient had the same G, but the P-R interval varied from 0.22 to 0.26 second. Statistically, the G of one normal person in several thousand may reach this magnitude. This is the largest G we have observed in an apparently quite normal electrocardiogram; but heart disease was probably present. The standardization was correct. We have, however, encountered one larger G from a presumably

normal heart recorded in the first edition of Graybiel and White's Atlas¹ (p. 33). This is a Wolfe-Parkinson-White syndrome. The gradient is, very approximately, 45.0 units, if the standardization, which is not shown, is correct. This patient had received quinidine, to stop a paroxysmal tachycardia which had persisted for two days. One is reminded of the large, abnormal, T waves sometimes observed after the cessation of a persistent paroxysmal tachycardia,¹² but here the T waves are upright in all leads. If there is myocardial "change," what is its localization?

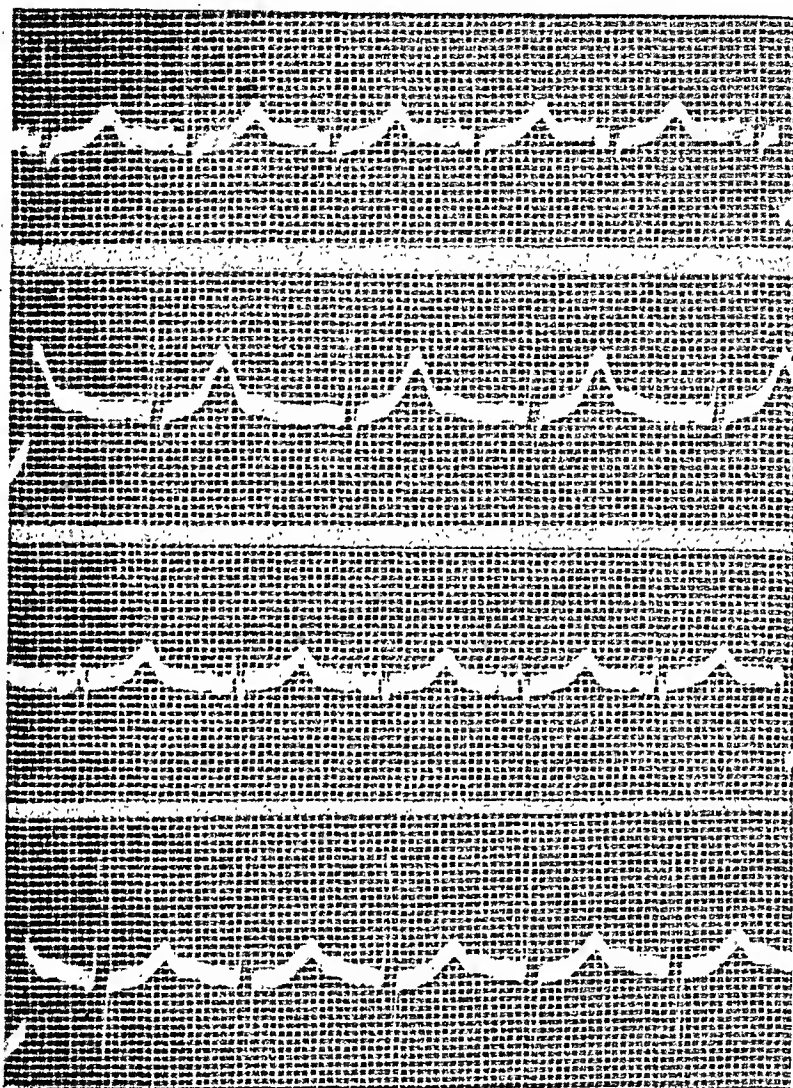


Fig. 4.—Colored woman aged 28 years. This case is described in the text. It may be noted that the ventricular gradient is deviated abnormally to the right.²

We have also seen one or two electrocardiograms with very high, but narrow T waves, which do not seem to belong in the category we are considering in this paper. Furthermore, examples from children's electrocardiograms are not included. Since the child's A_{QRS} is smaller than the adult's, although the mean G is the same,² the child's T wave is larger than the adult's, on the average.

DISCUSSION

In a case which was recently reported by Bayley, the RS-T segments of the electrocardiogram were depressed markedly, especially in Leads I and II.⁵ The depressions were larger than those which may often be ascribed to physiologic factors and were rather clearly indicative of injury. At autopsy it was found that damage of the subendocardial muscle laminae in the left ventricle was greater

than the damage of the subepicardial muscle layers. This paper gave the first direct evidence in man for a suspicion many students of electrocardiography have long entertained, namely, that preponderant subendocardial injury should depress the RS-T segments in two, or in all three, of the limb leads, depending upon heart position. Right ventricular injury may sometimes also do this, but in many cases there is no good evidence implicating that ventricle. In these negative or downward injury displacements we, therefore, see the converse of active pericarditis, which, as a rule, produces elevation of the RS-T segments in at least two limb leads.

✓ In a long series of experiments on the dog, Wolferth, Bellet, Livezey, and Murphy⁶ studied the effect of various procedures upon the RS-T segment with direct leading from the epicardial surface. Among other observations, they found that injection of a potassium chloride solution deep into the left ventricular wall, i.e., to the endocardial surface, produced a negative RS-T segment potential change at the overlying epicardial surface, but injection just beneath the epicardial surface produced an elevation. They also found that extensive trauma of the endocardial surface produced a negative RS-T segment displacement at the epicardial surface. Similar studies, but with indirect leading, have given no consistent results,⁷ although Boyd and Scherf⁸ picture very slight RS-T segment depressions in the limb leads, and state that no elevations occurred when the endocardium was injured. ✓

Bayley⁹ has given a definition of myocardial injury and of ischemia. In the *ischemic stage*, the intensity of polarization of the cell membranes is little, if at all, reduced, but repolarization during inscription of the T wave is slower than it normally is. Not all T waves of the so-called ischemic type, of course, are due to limitation in blood and oxygen supply; but it is very probable that the change in the fiber goes along with a similar, slow, chemical recovery in all cases. In the *injury stage*, the intensity of polarization of the cell membranes is reduced, and most injury displacements, as observed in the human electrocardiogram, are due to this. As Bayley and LaDue¹⁰ point out, both ischemic and injury changes are ante-mortem cellular changes, which disappear when circulation is restored. The electrocardiograms of many patients with coronary arterial disease or arterial hypertension reveal changes of the ischemic type, although there are no changes in the QRS complexes which suggest infarction. As a rule, the ischemic area appears to involve the epicardial (and probably the intramural) fibers more than the endocardial ones.⁹ If, then, the posterior wall is mainly involved, the T wave is inverted in Lead III and, usually, in Lead II. If the anterolateral wall is mainly involved, the T wave is inverted in Lead I, and sometimes in Lead II. The localizations are not in serious dispute, but it is by no means agreed that the endocardial surface is relatively less affected than the more superficial muscle layers.

High T waves in two or three of the limb leads, together with prolonged Q-T intervals, obviously suggest that in these rather rare cases we may be dealing with ischemia preponderantly affecting the inner surface of the left ventricle. None of the cases we report have come to autopsy, and, in view of the

minor nature of the pathologic change at the ischemic stage, as defined by Bayley, it is by no means certain that the microscope would reveal any difference between the different muscle layers in such cases.

Effects of Changing the Temperature of the Dog's Endocardium.—Experiments in which the temperature of the endocardium of the dog's ventricle was changed are reported at greater length elsewhere.¹³ The procedure was to introduce a stiff catheter into the dog's left ventricle by way of the left common carotid artery and aortic valve. At the moment the heart was arrested by faradization of the right vagus nerve, injection of 50 c.c. of Ringer's solution, at different temperatures in different experiments, was begun. Stimulation of the vagus was continued until all of the solution was injected. The purpose of arresting the heart was to permit the solution to come into contact with the endocardial surface of the ventricle and change its temperature before being pumped out. On other occasions the vagus was stimulated for the same length of time, and either no solution or solution at body temperature was injected. Either a limb lead electrocardiogram, or a precordial lead corresponding to the human CF₄, was recorded with each test or control. At the end of the series of experiments on each dog, the thorax was opened and the tip of the catheter was shown to be in the left ventricular chamber.

✓ It is well known that cooling a muscle slows, and warming accelerates, its repolarization. Thus cooling the endocardium should have the same effect as preponderant ischemia of the endocardial muscle layer.✓

The results of two experiments are illustrated in Figs. 5 and 6, and the temperatures at which the solution entered the syringe are given in the legend. It will be observed that in this dog the period of cardiac arrest alone produced no appreciable change in the height of the T wave in Lead II. In the chest lead, arrest was followed by a slight increase. ✓ The cold solution brought about a very large increase in the height of the T wave in both Lead II and CF₄ together with a large increase in the duration of the Q-T interval (Fig. 5). Warming had a smaller effect; yet it not only prevented the increase in the T-wave height due to the slowing in the precordial lead, but brought about a reduction in the amplitude (Fig. 6). In other experiments on another dog, the effect was greater, the T wave being definitely inverted by the warm solution, and the injection of Ringer's solution at 39°C. produced no appreciable change in the T wave. Rather consistently, the first beat after the release or escape from vagus stimulation, both with cooling and warming, showed less T-wave change than the second. The meaning of this is uncertain.✓

The results of cooling or warming the endocardium demonstrate that changes in the electrical state of that surface of the ventricle affect the form and amplitude of the T wave. They do not, of course, prove that the high and wide T waves in the human cases which we have reported in this paper are due to ischemic changes predominantly affecting the endocardial muscle layer of the left ventricle. They do, however, show that if such an endocardial change were to occur, it should be expected to increase the height and width of the T wave.

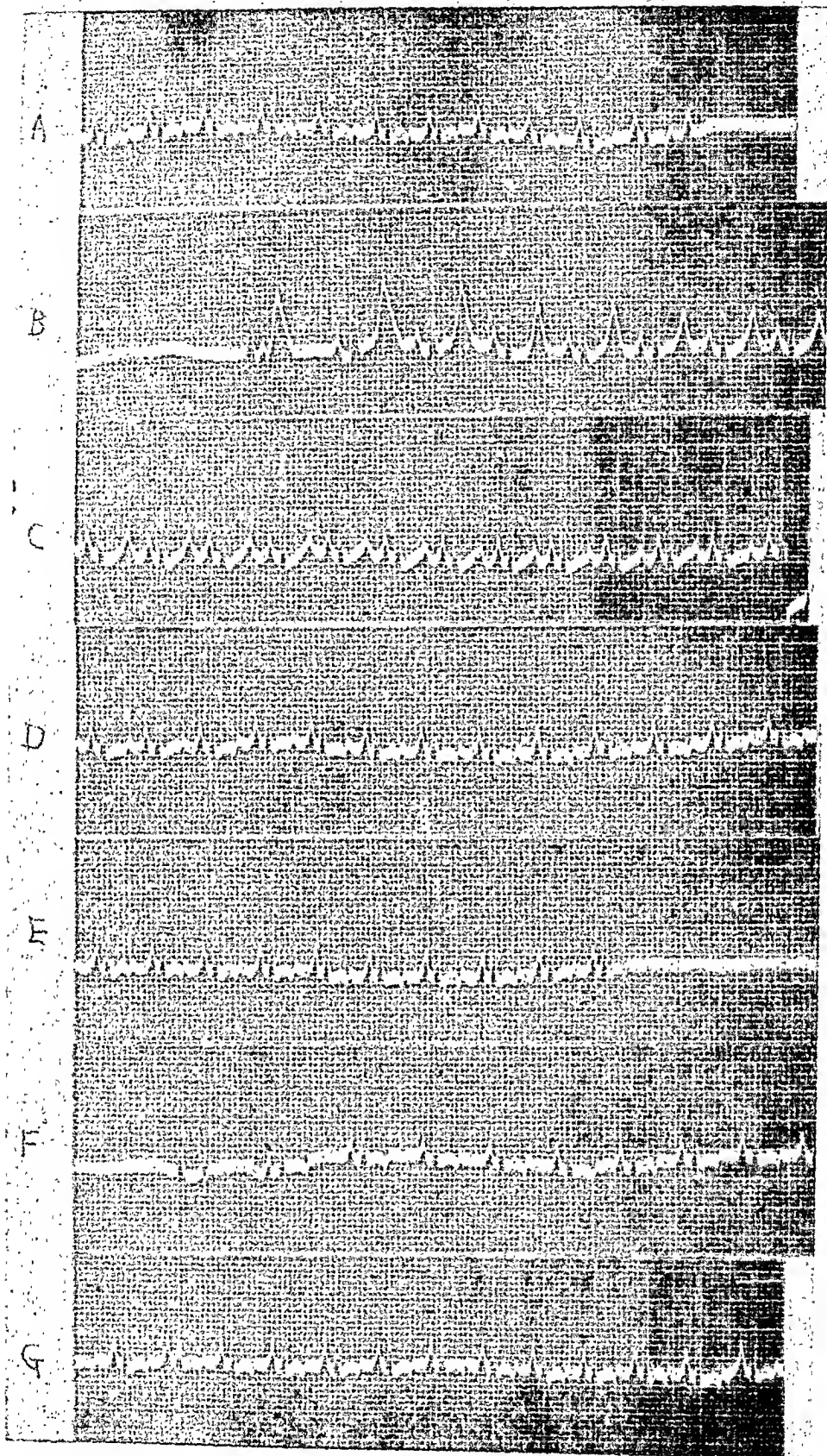


Fig. 5.—Effect of cooling endocardium of left ventricle. All Lead II. Same dog as Fig. 6.

At the end of Strip A, faradization of the right vagus was begun, together with injection into the left ventricular chamber of 50 c.c. of Ringer's solution, which entered the syringe at about 2°C.

Between A and B, four seconds of complete cardiac standstill are omitted. In B, injection completed and vagus stimulation stopped. There is a great increase in the height of the T waves, in spite of increased R waves. The Q-T interval is increased from 0.25 to 0.40 seconds. C and D are continuous with B.

In E, a few minutes after D, vagus stimulation begun, but no injection. Between E and F, four seconds of complete quiescence omitted. In F, stimulation stopped. The changes in the T waves are slight. (In other experiments, not with this dog, injection of Ringer's at body temperature produced no appreciable change). G is continuous with F.

The results of other control vagus stimulations in Lead II were practically identical with this one.

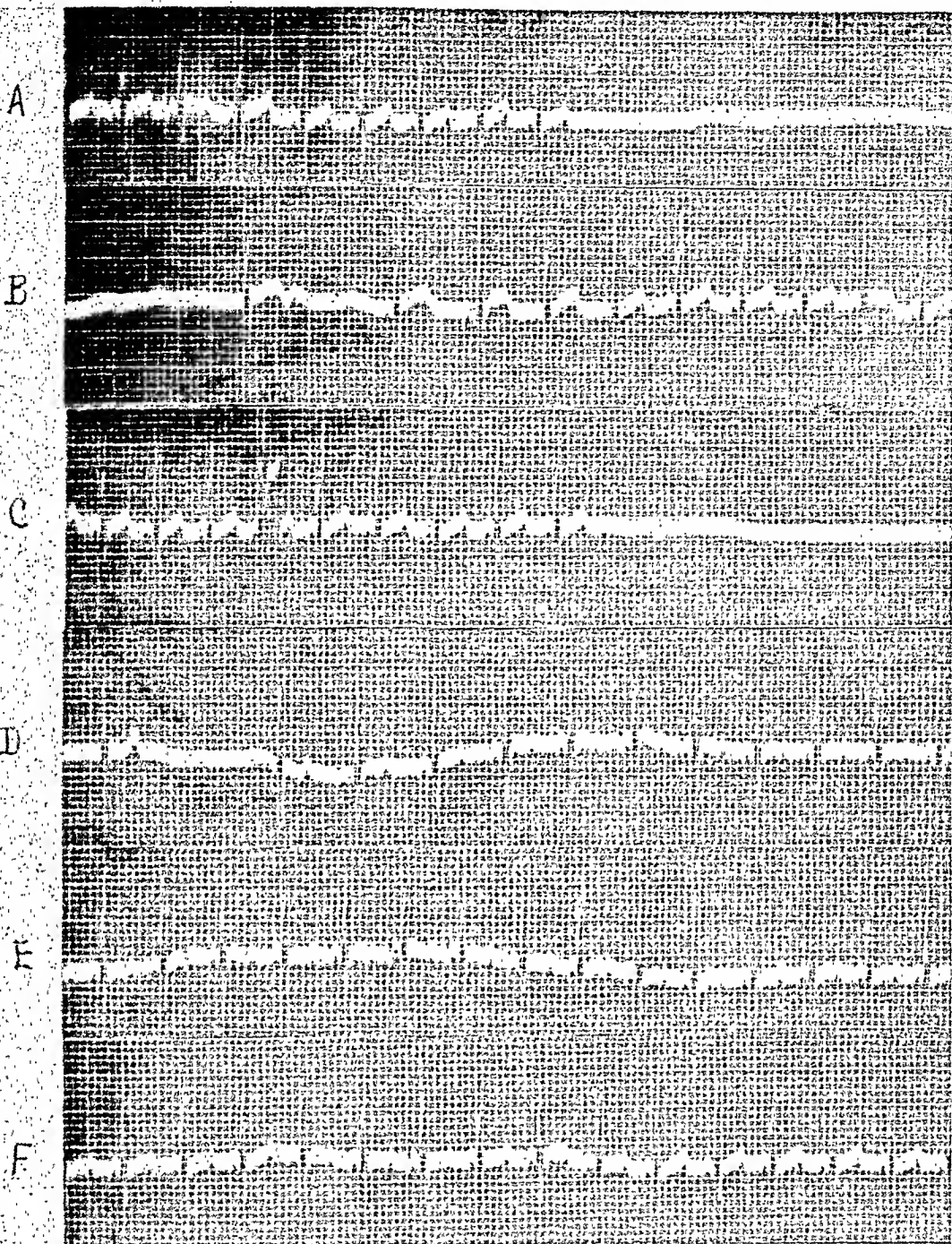


Fig. 6.—Precordial lead from a dog, approximately CF₄.

A shows the beginning of faradization of the right vagus nerve. Between A and B, just two seconds with no heart beats, are omitted. Vagus stimulation stopped early in B. No solution injected. Observe moderate increase in the T wave brought about by the cardiac arrest.

C, a few minutes later, shows the beginning of another period of right vagus stimulation. Just as the heart was arrested, the injection of 50 c.c. of Ringer's solution, which entered the syringe at 65°C., was begun. Between C and D, just two seconds of heart standstill are omitted. The first beat in D is an escape. The R wave of this beat is smaller and the S wave is larger than in other beats. The net area of QRS-T for this beat is reduced from the net area of the control. With return of heart activity later in D the reduction of the T waves is clear (compare the T waves of B). E and F are continuous with D.

A few minutes later, another control vagus stimulation was identical with A and B.

SUMMARY

It is suggested, on the basis of the experimental results of cooling or warming the endocardial surface of the dog's left ventricle, that large, upright T waves in the human electrocardiogram, together with prolongation of the Q-T interval,

may often be due to ischemic changes preponderantly involving the muscle layers at the endocardial surface of the left ventricle. The best examples of electrocardiograms of this type were obtained from patients with arterial hypertension and symptoms and signs of encephalopathy. Further study is needed before the reason for this association can be suggested.

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THE Q_3 AND QS_3 DEFLECTIONS IN THE ELECTROCARDIOGRAM: CRITERIA AND SIGNIFICANCE

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ALTHOUGH numerous studies have confirmed the pathologic significance of the Q wave in Lead III, first pointed out by Pardee,¹ this sign remains a subject of inquiry and some uncertainty. Occurring preponderantly in subjects with organic heart disease, particularly coronary artery disease, Q waves conforming to Pardee's criteria of abnormality are seen also in certain normal individuals, particularly in those in whom the heart lies transversely. In order to distinguish normal from pathologic Q waves in Lead III various modifications of Pardee's criteria have been recommended.²⁻⁵ Unipolar extremity leads, simultaneous registration of multiple limb leads,⁹ and esophageal leads¹⁰ have also been employed for this purpose.

Other problems complicate the interpretation of the Q wave in Lead III. Among these are its anatomic basis; the significance of Q_3 waves where marked respiratory variation occurs; the significance of small Q_3 deflections which do not meet fully Pardee's criterion, which requires Q_3 to have an amplitude equal to 25 per cent of the amplitude of the tallest QRS in the limb leads; the propriety of accepting as a Q_3 complexes preceded in some beats by a small initial upward deflection; and the significance of the QS_3 pattern and its relation to the Q_3 .

An attempt has been made to resolve some of these questions by reviewing a large source of material which appeared to be uniquely suited for such an analysis. A total of 1,355 subjects was studied, in all of whom the history, physical examination, and teleroentgenogram were reviewed, in addition to the electrocardiogram.

The following groups comprised the study.

1. Three hundred fifty-eight persons with Q waves in Lead III which conformed to the Pardee criteria. This group included (a) 103 insurance applicants with normal hearts; (b) 120 insurance applicants with hypertension or abnormal cardiac findings, such as enlargement of the heart or organic murmurs; and (c) 135 subjects with coronary artery disease who were receiving disability benefits. Most of the latter group had a history of coronary occlusion, but none of the electrocardiographic studies were made during the acute stages of infarction.

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2. Eight hundred persons with left axis deviation. This group was composed of (a) 239 insurance applicants who had normal hearts; (b) 261 insurance applicants with abnormal cardiovascular findings; and (c) 300 patients with coronary artery disease who were receiving disability benefits. This group of 800 subjects with left axis deviation was studied in order to establish the significance of absence of the S wave in Lead I, a finding which was found to augment the significance of a Q wave in Lead III.

3. Sixty-nine persons with a QS pattern in Lead III. This group included fifty-five insurance applicants and fourteen cardiac disability patients.

4. One hundred twenty-eight insurance applicants with small Q waves in Lead III, the amplitude of which was not equal to 25 per cent of the largest QRS deflection in the standard limb leads and did not, therefore, conform to the Pardee criterion.

Large Q Waves in Lead III.—The 358 cases with Q waves in Lead III which fulfilled Pardee's criteria were also analyzed for the presence of certain other characteristics of Q₃ and for certain accompanying findings. These characteristics and findings follow: (1) body build, in terms of overweight; (2) absence of S wave in Lead I; (3) presence of Q wave in Lead II (exceeding 1 mm. or 0.1 millivolt); (4) presence of Q wave in Lead II (exceeding 2 mm. or 0.2 millivolt); (5) slurring or notching of the QRS complex in Lead II; (6) low amplitude of the T wave in Lead II (under 2 mm. or 0.2 millivolt); (7) low amplitude of the T wave in Lead II (under 1 mm. or 0.1 millivolt); (8) inversion of the P wave in Lead III; (9) widened Q wave in Lead III (0.04 second or more in duration); (10) Q wave in Lead III (exceeding 5 mm. amplitude or 0.5 millivolt); (11) Q wave in Lead III, which equaled or exceeded 75 per cent of the amplitude of the tallest R wave in limb leads; and (12) deep inversion of the T wave in Lead III (exceeding 2.5 mm. or 0.25 millivolt).

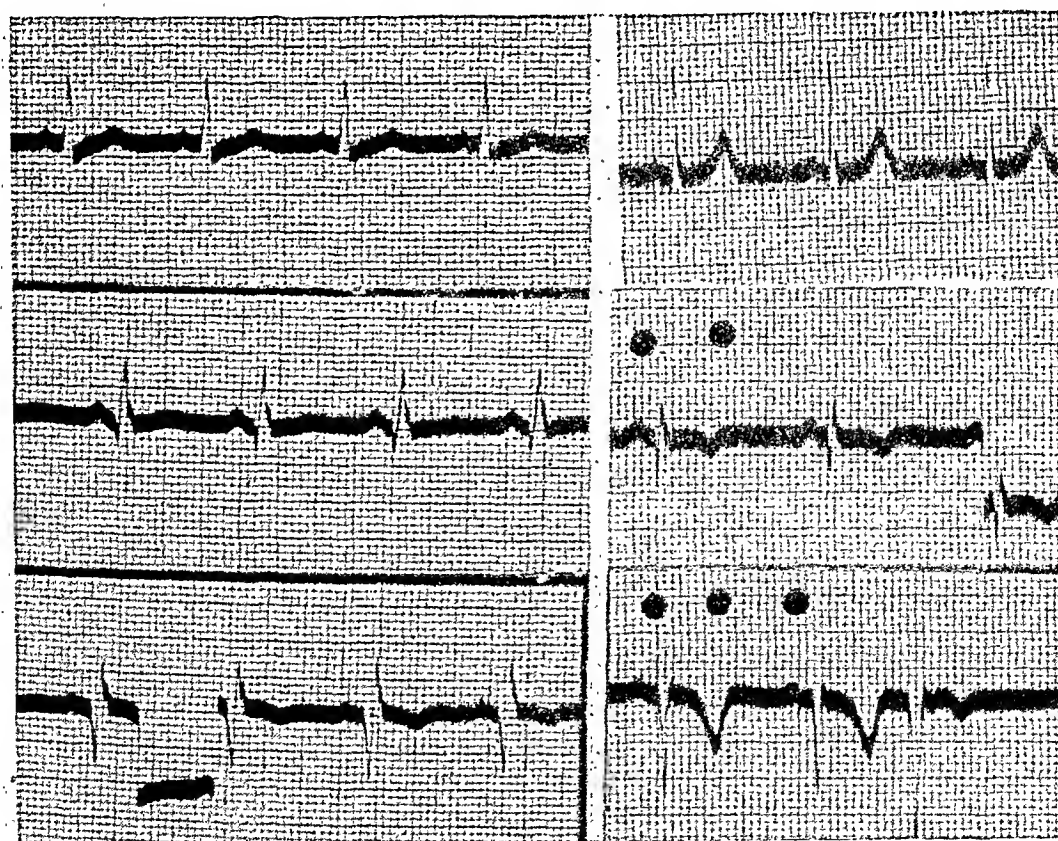
The findings are presented in Table I. The following appeared to offer a good differentiation between the "normal" Q₃ and the Q₃ due to coronary disease, since they occurred in 10 per cent or less of normal individuals with a Q₃ deflection, but were at least three times as frequent in the group with coronary disease with a Q wave in Lead III (Table I): (a) weight less than 5 per cent above normal; (b) absence of S wave in Lead I; (c) Q wave exceeding 1 mm. in Lead II; (d) low T wave in Lead II (less than 1 mm.); (e) wide Q wave in Lead III (.04 second or more in duration); (f) Q wave in Lead III, 75 per cent or more of the amplitude of the tallest R in the limb leads; and (g) deep inversion of the T in Lead III (exceeding 2.5 millimeters). (Fig. 1.)

The remaining variations studied showed definite difference in frequency of occurrence in normal subjects as compared with the group with coronary artery disease, but these criteria were less valuable in differentiating normal from pathologic Q waves in Lead III. The most significant distinguishing feature was found to be the presence of a low T wave in Lead II which occurred in only 3 per cent of normal subjects, but was present in 47 per cent of those with coronary artery disease. The presence of a Q wave in Lead II which exceeded 1 mm. was also found to be an important point of differentiation. This occurred in only

9 per cent of normal subjects, but occurred in 50 per cent of patients with coronary disease. Q waves exceeding 2 mm. were not observed in the normal group of 103 subjects, whereas they occurred in 27 per cent of the 135 patients with coronary disease. Absence of the S wave in Lead I, a sign to which no attention

TABLE I. ASSOCIATED CHANGES OCCURRING WITH THE Q_3 DEFLECTION

	NORMAL SUBJECTS— 103 CASES (PER CENT)	CORONARY DISEASE— 135 CASES (PER CENT)	ASYMPTOMATIC HYPERTENSION OR ABNORMAL CARDIAC FINDINGS— 120 CASES (PER CENT)
1. Weight less than 5% overweight	9	36	22
2. Absent S in Lead I	10	44	27
3. Q_2 exceeding 1 mm.	9	50	18
4. Q_2 exceeding 2 mm.	0	27	9
5. QRS_2 slurred or notched	14	34	19
6. T_2 under 2 mm.	36	87	39
7. T_2 low, under 1 mm.	3	47	13
8. P not inverted in Lead III	71	88	78
9. Q_3 wide (0.04 sec. or more)	5	17	7
10. Q_3 exceeding 5 mm.	17	32	30
11. Q_3 75% or more than tallest R	6	20	9
12. T_3 inversion exceeding 2.5 mm.	2	15	3



A.

B.

Fig. 1.—Two electrocardiograms of Q waves in Lead III which exhibit associated abnormal findings: Absent S_1 (B); Q_2 exceeding 1 mm. (A and B); Low T_2 (A); Wide Q_3 (A); Q_3 equaling or exceeding 75 per cent of the amplitude of the tallest R (B); Deep inversion of T_3 , exceeding 2.5 mm. (B).

has hitherto been paid, occurred in only 10 per cent of normal subjects with Q_3 waves conforming to the Pardee criteria, while it occurred in 44 per cent of patients with coronary disease. Widening of the Q_3 wave, large amplitude of Q_3 , and deep inversion of the T wave in Lead III, while they occurred rarely in normal subjects (5 per cent, 6 per cent, and 2 per cent, respectively), were less useful as a means of differentiating normal from pathologic Q_3 waves since they did not occur with significantly greater frequency in patients with coronary disease (17 per cent, 20 per cent, and 15 per cent, respectively). The material studied was insufficient to establish absolute validity of these latter three criteria as a means of distinguishing the normal from the pathologic Q_3 .

Employing the six electrocardiographic criteria found most useful (criteria b to g inclusive of the preceding tabulation, or headings 2, 3, 7, 9, 11, and 12 of Table I), it was found that 94 per cent of the patients with coronary artery disease exhibited one or more of these abnormalities. In contrast, one or more of these abnormalities was present in 50 per cent of the group with miscellaneous abnormal cardiac findings, and in only 24 per cent of normal subjects with a Q wave in Lead III which conformed to Pardee's criteria.

The presence in the standard limb leads of one or more of the abnormalities which have just been discussed appears, therefore, to offer a satisfactory means of distinguishing the so-called normal from the pathologic Q wave in Lead III in the majority of cases. The association of such abnormalities would appear, further, to lend added significance to "indeterminate" Q waves in Lead III where an initial small upstroke precedes the initial downward deflection in some beats.

Absence of the S Wave in Lead I.—In analyzing the various electrocardiographic variations occurring with the Q wave in Lead III, it was observed that in 90 per cent of normal individuals with a Q in Lead III, an S wave was present in Lead I. In seventeen subjects with large Q waves in Lead III due to pregnancy, reported by Carr, Hamilton, and Palmer,¹¹ an S wave was present in Lead I in all instances. In contrast, in the present study S waves in Lead I were found to be lacking in fully 44 per cent of patients with a Q_3 due to coronary disease. Accordingly, a study was made to determine the significance of absence of the S in Lead I without regard to the presence of a Q in Lead III. For this purpose 800 cases with left axis deviation were studied. The source of the material was as follows: 239 insurance applicants with normal hearts; 261 insurance applicants with abnormal cardiac findings; and 300 patients with coronary artery disease who were receiving disability benefits. The findings are summarized in Table II. In normal individuals with left axis deviation, absence of an S wave in Lead I was infrequent, occurring in only 18 per cent of the subjects studied. In patients with heart disease accompanied by left axis deviation, absence of the S wave in Lead I was very frequent. It appears to be associated with left ventricular enlargement, since it occurred in 44 per cent of patients with early hypertension, and in fully two-thirds of patients with advanced hypertension who had left axis deviation. While not specific, it is by far the most frequent electrocardiographic variant accompanying left axis deviation.

tion in left ventricular hypertrophy, occurring twice as often as any other electrocardiographic abnormality. Thus, in 100 patients with teleroentgenographic evidence of left ventricular enlargement which exhibited left axis deviation, an absent S wave in Lead I was observed in 64 per cent, while depression of the S-T in Lead I was present in 33 per cent, T_1 abnormalities in 30 per cent, high voltage of the QRS in 29 per cent, and other abnormalities in the ventricular complex in 27 per cent of cases.

TABLE II. ANALYSIS OF 800 CASES WITH LEFT AXIS DEVIATION, WITH REFERENCE TO S WAVE IN LEAD I

	NUMBER OF CASES	S_1 PRESENT	S_1 BORDERLINE	S_1 ABSENT
Normal heart	239	159 (67%)	36 (15%)	44 (18%)
Early heart disease				
Nonhypertensive	90	36 (40%)	14 (16%)	40 (44%)
Hypertensive	171	71 (41%)	25 (15%)	75 (44%)
Advanced heart disease				
With hypertension and enlargement				
By x-ray	100	25 (25%)	11 (11%)	64 (64%)
By electrocardiogram	100	23 (23%)	7 (7%)	70 (70%)
Coronary disease, anginal syndrome (no enlargement)	100	44 (44%)	9 (9%)	47 (47%)

It appears, therefore, that absence of the S wave in Lead I may be significant quite apart from its association with a Q wave in Lead III. However, its occurrence in 18 per cent of normal individuals with left axis deviation indicates that this sign is not a sufficiently specific abnormality to be of diagnostic value independent of other electrocardiographic findings.

The QS Pattern in Lead III.—Sixty-nine persons were studied who exhibited a QS pattern in Lead III. Of these, fourteen were cases of cardiac disability (advanced heart disease) and the remaining fifty-five were applicants for insurance. Forty-three of these fifty-five persons had heart disease or hypertension and only twelve showed no evidence of heart disease. The incidence of heart disease in persons with a QS_3 pattern (78 per cent) was considerably greater than the incidence of heart disease in an unselected group of two hundred six insurance applicants with left axis deviation (40 per cent). The occurrence of a QS_3 pattern is associated with left ventricular hypertrophy in the majority of instances. Fifty-one of the total of sixty-nine subjects with a QS_3 pattern had hypertension and electrocardiographic or roentgenologic signs of left ventricular hypertrophy.

In effect, the QS_3 pattern is equivalent to a Q_3 plus an absent S_1 . Of the sixty-nine cases with the QS_3 pattern, S_1 was absent in fifty-six cases, and in the remaining thirteen S_1 was small and did not exceed 2 mm. (0.2 mv.) in any case.

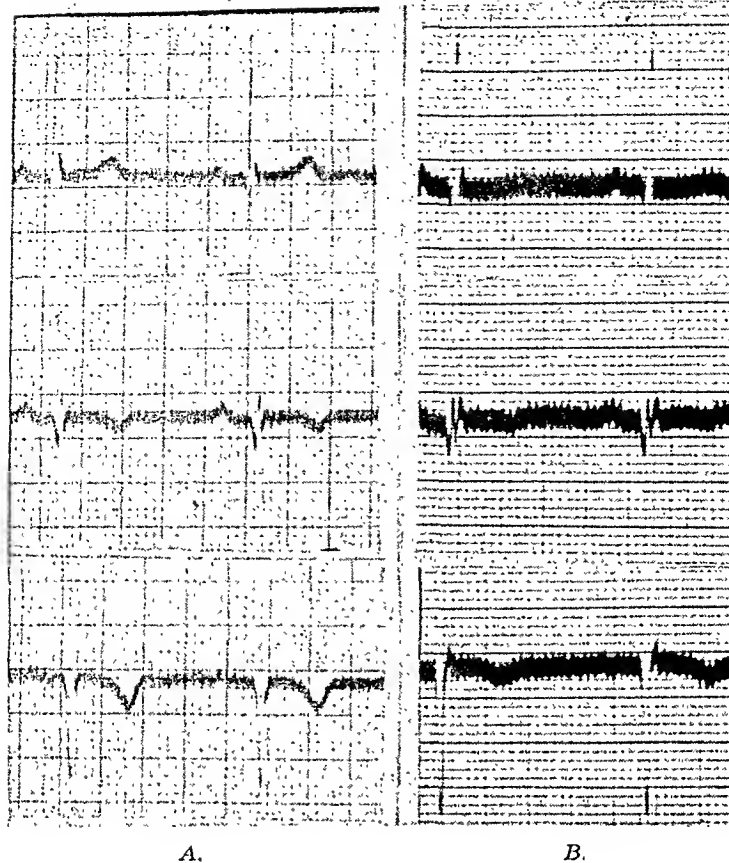


Fig. 2.—QS₃ pattern with associated Q₂. The second tracing (B) made a year following (A) shows a change from a QS₃ to Q₃ pattern.

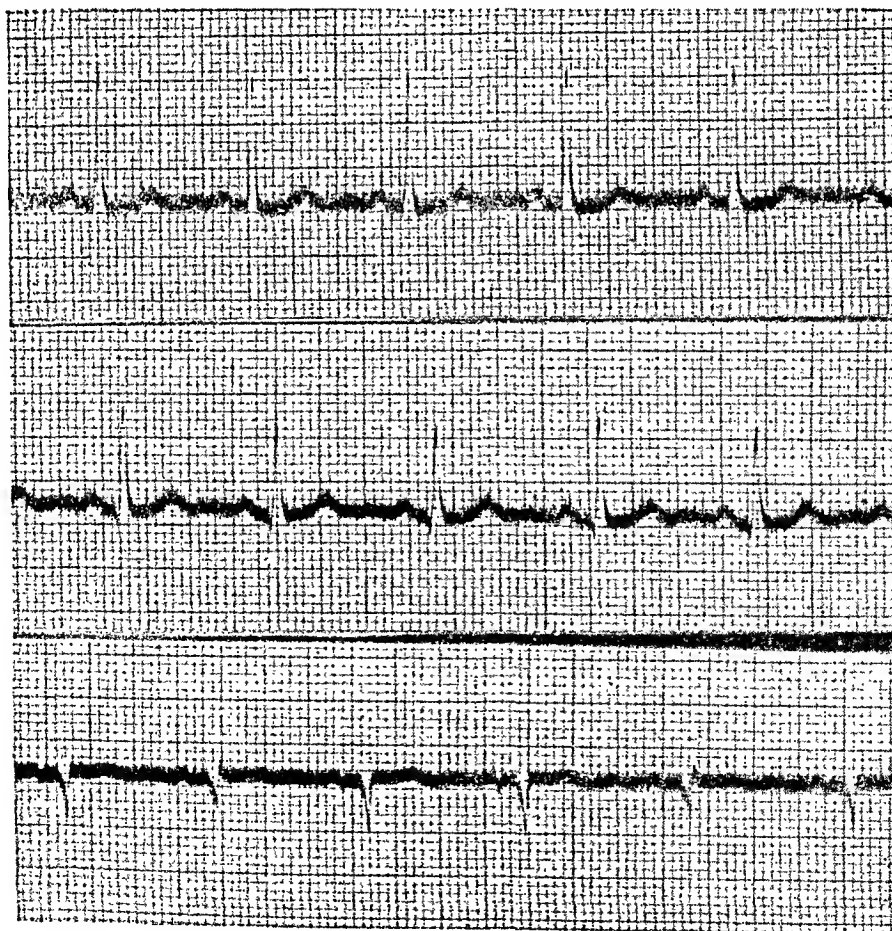


Fig. 3.—QS₃ pattern alternating with Q₃ pattern.

Evidence that the QS_3 pattern is closely related to the Q_3 pattern is seen in the frequent association of a Q in Lead II (Fig. 2), and in the transition in successive beats of the QS_3 to the Q_3 pattern (Fig. 3).

Small Q Waves in Lead III.—Analysis was made of 128 cases with a small Q_3 which did not fully conform to Pardee's criterion in that the amplitude was less than 25 per cent of the maximal QRS deflection in the limb leads. These were studied in four groups, each composed of thirty-two cases. A small Q_3 was common to all four groups. Group 1 showed, in addition, an absent S_1 with tendency to left axis deviation; Group 2, a tendency to left axis deviation (R_1 greater than R_3); Group 3, a normal electrical axis; and Group 4 showed right axis deviation. Only Group 1 (small Q_3 associated with absent S_1) showed a significantly high incidence of heart disease, nineteen of thirty-two cases. Twelve of these nineteen patients had hypertension, two died of coronary occlusion shortly after they were studied, three had an organic apical systolic murmur, one had aortic stenosis, and one patient exhibited marked T-wave abnormalities in the electrocardiogram.

These findings suggest that a small Q wave in Lead III should not be considered significant unless accompanied by an absent S wave in Lead I.

COMMENT

The employment of specialized electrocardiographic techniques, particularly unipolar extremity potentials, has contributed much to a better understanding of the Q_3 wave. It has been shown with this technique⁶⁻⁸ that the Q_3 due to myocardial infarction is the result of potentials distributed to the left leg electrode, whereas the Q_3 found in normal individuals has a different genesis. In this presentation we are stressing the desirability of attempting to obtain more definitive information concerning the Q_3 wave from the information furnished by the standard limb leads. In doing this, we have no desire to deprecate the use of specialized techniques. The present study demonstrates that differentiation of the normal from the pathologic Q_3 is usually possible if the criteria which were found to be most useful in this analysis are applied.

Several of the accompaniments of the Q_3 which add significance to this wave have been previously pointed out. These include the presence of a Q in Lead II² and an increased duration of the Q_3 .⁴ Attention does not appear to have been called, hitherto, to the added significance of absence of an S wave in Lead I, a frequent finding in the patients of this series who had heart disease. In contrast, an S wave in Lead I is generally present in persons with "normal" hearts who show Q waves in Lead III, for example, in pregnant women. Independent of an association with a Q_3 , absence of the S wave in Lead I is a relatively infrequent finding in normal individuals with left axis deviation, whereas it is extremely common in the presence of heart disease, particularly left ventricular hypertrophy. Unfortunately, this sign is not sufficiently specific to be of definite diagnostic value in itself. However, it lends added significance to the Q_3 ; even when the Q_3 is of small amplitude, the association with an absent

S_1 strongly suggests the presence of an abnormal heart. The QS_3 pattern in effect amounts to a Q_3 plus absent S_1 and is at least as significant as the deep Q_3 alone.

An attempt was made to carry out a follow-up study of mortality. However, it was possible to reinvestigate only seventeen cases who died, a number too small for statistical purposes. In all of these seventeen persons, Q_3 was the only abnormal finding on examination for insurance. The electrocardiogram was taken, in most instances, because of the large amount of insurance for which application was made. Q_3 waves of four types were included in this study: (1) Q_3 with accompanying electrocardiographic changes of significance, as indicated in the present study. There were five patients in this category, all of whom died of coronary artery disease at intervals varying from one and one-half to nine years after the electrocardiogram was made. The average survival period was 4.4 years. (2) Q_3 deflections which conformed to the Pardee criterion, but were not accompanied by other abnormalities. Five patients of the series fitted into this category. Four of these five patients died of heart disease and one died of pneumonia. The average survival period was 5.5 years. (3) Q_3 deflections which exhibited marked respiratory variation. Three of the four patients who showed this finding died of heart disease and one died of cerebral thrombosis. The average survival period was 7.1 years. (4) Small Q_3 deflections which did not fully conform to the Pardee criterion. All three patients with this type of Q wave died of heart disease. The average survival period was 6.5 years.

While no valid statistical conclusions can be drawn from such a small number of cases, the unusually high incidence of deaths from heart disease (15 of 17 cases) is striking. Even among the patients with presumably normal hearts in whom the Q_3 appeared due to transversely placed hearts and obesity, the high incidence of death from heart disease is remarkable. The full significance of these findings must await analysis of a much larger experience. However, this small sample suggests that a Q_3 is an unfavorable prognostic sign, and even in the presence of obesity, marked respiratory variations, or relatively small amplitude of the Q_3 , it becomes questionable whether this sign can be lightly dismissed as a normal variant.

Different mechanisms appear to operate in causing each of the three different types of Q deflections which may be observed in the electrocardiogram: (1) the Q wave due to infarction, (2) the small Q deflections which are observed normally, and (3) the deep Q_3 which occurs in normal subjects with horizontally placed hearts. The deep Q_3 or QS_3 frequently observed in left ventricular hypertrophy probably arises from a mechanism similar to the mechanism which produces it in horizontal position of the heart.

The mechanisms of origin of Q waves may be visualized by the schematic representations in Fig. 4.

1. In myocardial infarction, as Wilson¹² has shown, an infarct which involves the entire thickness of the ventricular wall acts as a window, so that the negativity of the interior of the ventricular cavity is transmitted directly to the surface of the body. The surface electrode, therefore, registers a potential similar

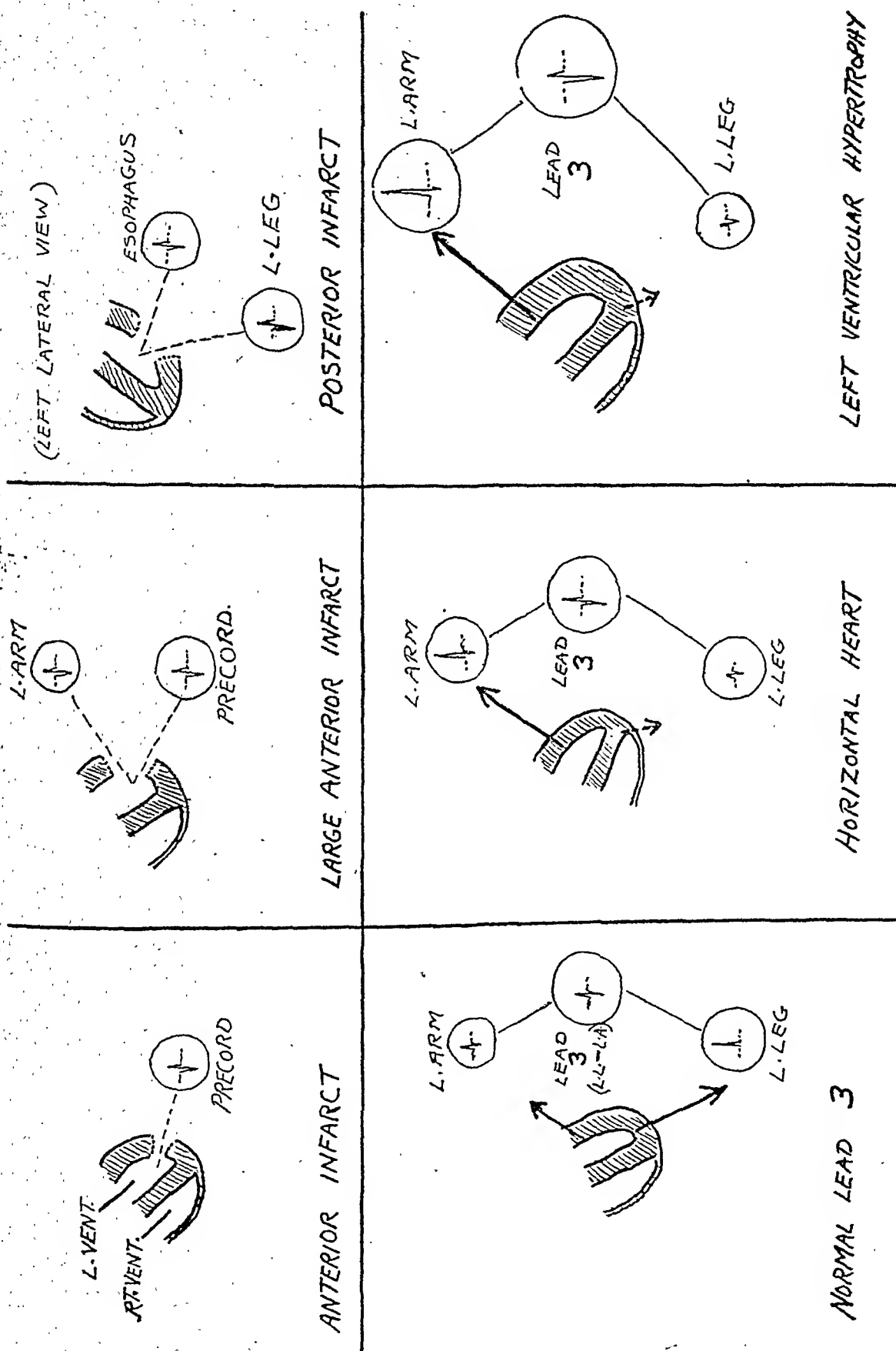


Fig. 4.—Mechanisms of origin of Q waves in infarction, in horizontal position of the heart, and in left ventricular hypertrophy. The infarct acts as a "window" so that leads in the path of the "window" act as somidirect leads from the interior of the ventricular cavity. recording the initial negative potential of the ventricular cavity. In anterior infarction this is detected by precordial leads. If the infarct is large, a deep Q will appear over a wide area of the left chest wall and also in the left arm, appearing as a Q in Lead I. In posterior infarction, the initial negative potential is transmitted to the leads from the left leg and esophagus. When the heart is transversely placed an increased positive potential is registered in the left arm lead producing greater negativity of Lead III (left leg minus left arm potential). This may appear as a deep S or deep Q in Lead III. This is further accentuated in left ventricular hypertrophy.

to that recorded by an electrode placed within the interior of the ventricular cavity. In anterior infarction, the negativity of the interior of the ventricular cavity is transmitted to leads directly over the precordium, and, when the infarct is large, to the left arm as well, resulting in a Q wave in the standard Lead I. In posterior infarction, located on the under surface and posterior surface of the heart, the negativity of the ventricular cavity is transmitted inferiorly to the left leg, and posteriorly where a Q wave may be recorded in esophageal leads.

2. The small Q deflection which is observed in persons with normal hearts is probably due to the very early activation of the left side of the interventricular septum^{13,14} with passage of the impulse from the left to the right side of the septum at a time before any other ventricular excitation occurs. Since passage of electrical activity away from a point of registration is recorded as negativity,* whereas electrical activity flowing toward a point of registration is recorded as a positive potential, leads from the left side of the septum (left arm and left leg) will exhibit a small negative deflection (Q wave), which reflects passage of electrical activity through the septum away from these points of registration on the body surface. As soon as the excitation wave reaches the lateral ventricular wall and begins passage externally a positive deflection, or R wave, succeeds the small Q in these leads.

3. The deep Q₃ seen in normal individuals with horizontally placed hearts is not a Q wave in the true sense, since it is not due to negativity of the interior of the ventricle as is the Q₃ due to infarction or the small normal Q deflection. Standard Lead III is the resultant potential of unipolar extremity leads of the left arm and left leg. Lead III expresses the potential of the left leg minus the potential of the left arm, where the potential of the left arm is expressed as a negative quantity. Therefore, the more positive the potential of the left arm and the less positive the potential of the left leg, the more negative is the excitation wave as recorded in Lead III. In the normally placed heart the direction of potential is illustrated in Fig. 4. A positive potential is transmitted both to the left leg and left arm; and Lead III (left leg minus left arm) is still positive, or slightly negative (normal left axis deviation). In the transversely placed heart (Fig. 4) a much greater positive potential is transmitted to the left arm. Only a small positive potential, or even a negative potential, is transmitted to the left leg, since the direction of the excitation to the greater part of the ventricle may be away from the left leg. The resultant Lead III (left leg minus left arm), as Myers and Oren⁷ have pointed out, may exhibit a deep S wave (left axis deviation), or even a deep Q or QS deflection. In hypertrophy of the left ventricle, the thickened left ventricle will further accentuate the degree of left axis deviation and appearance of a deep Q or QS deflection, because of the augmented positive potential in the left arm electrode.

It is seen in Table I (Column 3) that the characteristics of the Q₃ deflection in subjects with hypertension more closely resemble the "normal" Q₃ than the

*It is for this reason that the potential of the interior of the ventricular cavity is negative throughout excitation: the impulse is passing outward from the interior of the ventricular wall. In this discussion of the excitation wave only the left ventricle and interventricular septum are considered. The contribution of the thin right ventricle to the excitation wave is ordinarily small and may be disregarded.

Q_3 due to coronary disease (previous posterior infarction). The association of a large Q_3 with left ventricular hypertrophy in the absence of a history of infarction, a striking finding in the present series, has been noted previously. Thus, in autopsies on nine patients with a large Q_3 reported by Willius,¹⁵ considerable left ventricular hypertrophy was present in all but one. The fact that the hearts of four patients showed no changes in the coronary arteries was considered by Willius to support the view that left ventricular hypertrophy was the dominant factor in the genesis of the Q wave in Lead III. Similar observations were made by France.¹⁶ In twelve patients with a large Q_3 deflection on whom necropsy was performed, infarction was present in only five, whereas hypertrophy was present in all but two of the twelve.

SUMMARY AND CONCLUSIONS

An analysis of a large series of cases was undertaken to establish criteria of abnormality of the Q_3 deflection in the electrocardiogram. Certain findings appear to aid in the differentiation of the "normal" Q_3 and the Q_3 due to coronary disease. The findings which follow were found to be present in 10 per cent or less of normal individuals with a Q_3 wave conforming to Pardee's criterion. They were present at least three times as frequently in subjects with a Q_3 due to coronary disease.

- (a) Weight less than 5 per cent overweight.
- (b) Absence of S wave in Lead I.
- (c) Q wave exceeding 1 mm. in Lead II.
- (d) Low T wave in Lead II (less than 1 mm.).
- (e) Wide Q wave in Lead III (0.04 second or more in duration).
- (f) Q wave in Lead III which equals or exceeds 75 per cent of the amplitude of the tallest R in the limb leads.
- (g) Deep inversion of the T wave in Lead III (exceeding 2.5 mm.).

In order of importance the features which were most significant of an abnormal Q_3 were found to be a low T wave in Lead II, the presence of a Q in Lead II which exceeded 1 mm. in amplitude, and an absence of an S wave in Lead I. Employing the six electrocardiographic criteria (b-g), it was found that 94 per cent of patients with a Q wave in Lead III due to coronary artery disease exhibited one or more of these abnormalities, while only 24 per cent of normal subjects with a Q_3 conforming to Pardee's criterion showed one or more of these findings. The presence of one or more of these abnormalities in the standard limb leads offers a satisfactory means of distinguishing the so-called normal from the pathologic Q wave in Lead III.

Absence of the S wave in Lead I not only confers added significance to a Q_3 deflection, but may be of some significance without relation to its association with a Q_3 deflection. It appears to be associated with left ventricular enlargement, since it was present in fully two-thirds of the patients with advanced hypertension who exhibited left axis deviation. The occurrence of this finding in 18 per cent of normal individuals with left axis deviation indicates that ab-

sence of S_1 is not a sufficiently specific abnormality to be of diagnostic value of itself. While not specific, it is by far the most frequent electrocardiographic variant accompanying left axis deviation in left ventricular hypertrophy, since an absent S in Lead I occurred twice as often as any other electrocardiographic abnormality. The QS_3 pattern is closely related to the Q_3 pattern and is, in effect, equivalent to a Q_3 plus an absent S_1 . Small Q waves in Lead III, not conforming in amplitude to Pardee's criterion, are not significant unless there is also an absence of the S wave in Lead I.

A limited mortality study suggests strongly that the Q_3 deflection is a significant abnormality which should not be dismissed simply because of associated overweight and transverse position of the heart. Fifteen of seventeen cases with no cardiovascular abnormalities other than a Q_3 deflection died of heart disease, after an average survival period for the entire seventeen cases of 5.7 years. The duration of life was shortest (4.4 years) in a group of five cases in which the Q_3 pattern was accompanied by electrocardiographic findings which are indicated by this study to increase the significance of the Q_3 deflection.

Different mechanisms are concerned in the genesis of the Q_3 wave due to infarction, on the one hand, and the Q_3 and QS_3 deflection which may occur in the horizontally placed heart and in left ventricular hypertrophy, on the other. The mechanisms of origin of the normal small Q wave, the Q wave due to infarction, and the Q_3 and QS_3 deflections due to horizontal position of the heart and left ventricular hypertrophy are discussed.

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COMPARATIVE STUDY OF THE INTRACAVITY POTENTIAL IN MAN AND IN DOG

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THERE is very little literature on cardiac intracavity potentials recorded with unipolar leads. Wilson and associates,¹ working on dogs, were the first to point out that the left intraventricular record shows an exclusively negative QRS complex (complex QS). In the intracavity record of the right ventricle, there may appear an initial positivity (R wave) preceding the great negative complex. This positive deflection has been attributed to septal activation. Wilson and co-workers² described the changes in the shape of the intraventricular records after the production experimentally of bundle branch block. When there is left bundle branch block, the negativity disappears from the left cavity and the record is that of the RS type; the right cavity potential is exclusively negative (QS). If the block is produced on the right side, the left intraventricular potential remains exclusively negative (QS), and that from the right cavity is of the RS type. One of us³ studied in dogs the modification of the negative intracavity potential in the left ventricle after ligation of the anterior descending artery. Wolferth and associates⁴ studied the displacement of the RS-T segment of intracavity records in different experimental conditions. They did not find displacement of that segment after the ligation of the coronary vessels. Lenegre and Maurice⁵ described the intracavity leads in the right auricle and ventricle of the human heart. Recently, Hecht⁶ studied the morphology of the intracavity tracings recorded from the right auricle and ventricle and analyzed the results on the basis of the dipole theory. We know of no other publication related to the intracavity potentials obtained with unipolar leads.

This study was undertaken to amplify our knowledge of the intracavity potential. It embraces (1) the intracavity potential of the dog in different experimental conditions (the four cavities of the heart were studied) and (2) the potentials of the right cavities of the human heart, in normal and pathologic conditions.

THE INTRACAVITY POTENTIAL OF THE DOG

The following points were studied:

1. Left intraventricular potential after ligation of the anterior descending artery (with particular reference to displacement of the RS-T segment).

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From the National Institute of Cardiology of Mexico.

2. Left intraventricular potential after ligation of the left circumflex artery (with special reference to the RS-T segment).
3. Right and left intraventricular potentials during the production of ventricular extrasystoles.
4. Intracavity potentials in right bundle branch block.
5. Intracavity potentials in left bundle branch block.
6. Intraventricular potentials in complete heart block.

Material and Method.—The experiments were carried out in dogs under nembutal and urethane. The anesthetic solution (50 Gm. of urethane dissolved in distilled water to which 20 Gm. of nembutal were added to 200 c.c. of water) was injected intraperitoneally (1 c.c. per 3 kilograms of body weight). Artificial respiration was given either by tracheotomy or by tracheal intubation with a Foregger catheter. In all dogs the heart was widely exposed by opening the chest down the mid-line, from the xiphoid appendix to the interclavicular symphysis.

After opening the pericardium, the serous membrane was sutured to the costal wall in order to form a cradle for the heart. The electrodes used were similar to those already described by one of us.³ The silver chloride intracavity electrodes were sometimes covered with cotton. Records were taken from the epicardium by attaching the cotton wicks of the electrodes to the epicardium by means of thin threads, being very careful not to damage the underlying muscle. For the intracavity leads, the electrodes were introduced through the auricular appendix. Since the left auricular appendix, lying toward the back, is difficult to reach, it is convenient to open a window in the costal wall in order to make the operations easier. Some of the records from the right cavities were obtained by introducing a special electrode through the femoral vein into the heart. In many of the experiments it was possible to control the intracavity position of the electrode by feeling it through the muscular wall. At the end of the experiment the position of the electrode was always verified.

The left circumflex artery was ligated near the origin of the vessel. The anterior descending artery was ligated before it begins to branch.

In order to sever the right bundle branch, a thin knife was introduced through the right ventricular wall, near the auriculoventricular sulcus, at a point between the emergence of the anterior descending artery and the right auricular appendix. It is very important to note that the point of the instrument must be directed toward the interventricular septum at an angle of approximately 45 degrees to the horizontal line. The incision, following Lewis's method,⁷ was made just beneath the septal segment of the tricuspid valve. For a depth of 2 mm. the incision should be 0.5 cm. long.

The section of the left bundle branch is technically more difficult than that of the right. The knife must be introduced in the angle formed by the left anterior descending artery and the diagonal branch one. Afterward, when the blade is inside the left ventricular cavity, it is directed toward the aortic ostium, being slipped near the interventricular septum in order to avoid the obstacle constituted by the internal leaflet of the mitral valve. It is helpful for the in-

vestigator to place the index finger of the left hand at the base of the heart, at the sulcus formed by the right auricular appendix and the posterior face of the aorta, and to direct the knife toward that finger. When the pressure of the knife is felt by the index finger through the aortic wall, the instrument is at a point above the aortic semilunar valve; the knife is then lowered a little in order to make the section. By means of this operation, it is also possible to perform the total division of the bundle of His in order to get complete heart block.

In order to avoid severe hemorrhage, a small suture can be made in the place where the knife is introduced; generally, however, compression of the wound is sufficient, as the myocardial muscular tone causes hemostatsis.

All the records obtained directly from the heart were taken with unipolar leads; the indifferent electrode was placed on any of the legs. They were always standardized so that 3 mv. produced a 2 mm. deflection.

Left Intraventricular Potential After Ligation of the Anterior Descending Artery, With Special Reference to Deviation of the RS-T Segment: One of us³ has stated that the form of the intracavity potential in the left ventricle is practically unmodified by the ligation of the anterior descending artery. On that occasion the possibility was suggested that the position of the exploring electrode in relation to the injury zone might have been inadequate to register the shift. We have already said that Wolferth and associates⁴ did not find any deviation of the RS-T segment of the intracavity records after ligation of the coronary vessels.

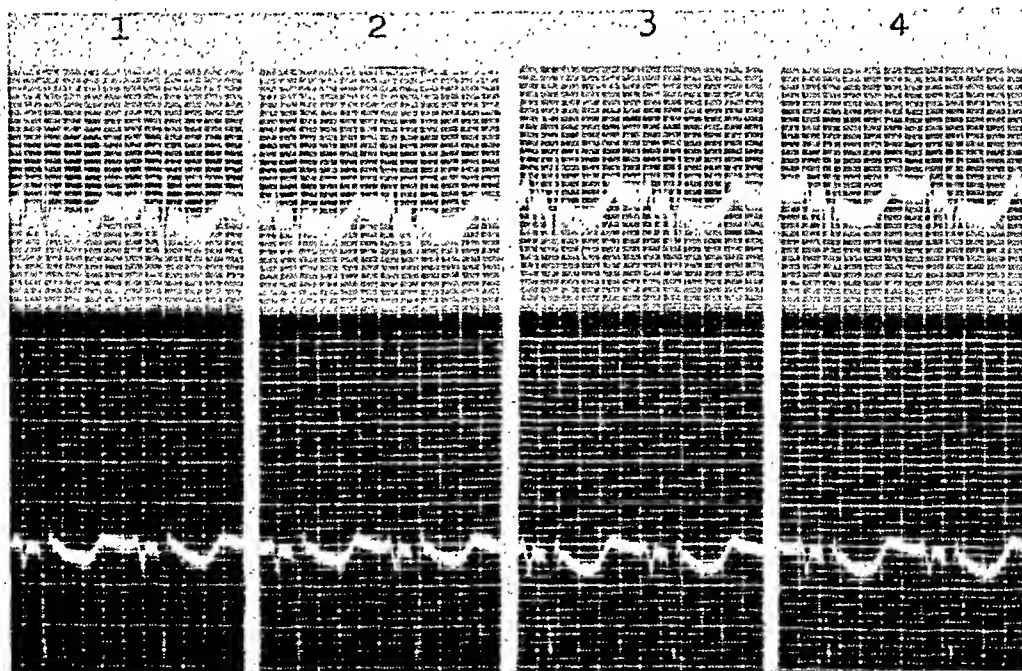


Fig. 1.—Unipolar intracavity tracings after ligation of the anterior descending artery. The upper row shows the tracings obtained when the exploring electrode was in contact with the posterior surface of the heart on a point opposite the infarction. The lower row shows the left intraventricular tracings, taken ninety minutes (1), one hundred minutes (2), one hundred ten minutes (3), and one hundred twenty minutes (4) after the ligation. Notice the negative displacement of the RS-T segment in both tracings.

After several experiments, we concluded that the negative results (thus far obtained) were due to the special position of the exploring electrode in relation to the zone of injury. This view was confirmed when we found that ninety minutes after ligation of the anterior descending artery we could obtain a negative displacement of the RS-T segment in the left intraventricular tracing (Fig. 1). Tracings taken from the posterior epicardial surface of the left ventricle show a downward displacement of the RS-T segment similar to that of the endocardial pattern (Fig. 1). In the post-mortem study we were able to prove that the intracavity exploring electrode was on the posterior surface and opposite the infarcted zone. This situation explains the striking resemblance of the RS-T patterns in the intracavity and extracavity tracings. The negative results obtained by some authors are easily explained if we take into consideration the difficulties of controlling the exploring electrode. The data can be explained according to the ideas of Bayley,⁸ which relate them to a vector directed from the center of the affected ventricle to the center of the injured zone. When the intracavity electrode is opposite to the zone of the infarction, the injury potential (RS-T) registered by it, is negative, because it is oriented toward the negative pole of the vector. Epicardial potentials of the posterior surface with a similar orientation have the same morphology as those of the intracavity pattern. Anterior epicardial potentials in the injury zone are positive and of greater voltage. On different occasions we have found (in post-mortem examinations) that the exploring electrode was in contact with atrioventricular valves. In this position its direction is nearly perpendicular to the spatial axis of injury; in such instances it is very difficult to record the shift of RS-T.

Left Intraventricular Potential, After the Ligation of the Left Circumflex Artery, With Special Reference to the RS-T Segment: In this type of experiment changes in the RS-T segment were very easily obtained, in contrast to the results of the experiments in which the anterior descending artery was ligated. These changes were mainly of two types.

1. In a minority of the cases there was positive displacement of RS-T in tracings made from the epicardial surface of the zone of infarction. On the other hand, the endocardial variations were not conspicuous. In Fig. 2, the upper records are epicardial and were registered in the zone of infarction. The control shows a RSR type complex, in which the second upward component is smaller than the preceding components, with negative T wave and a rise of the J point. After the ligation, positive displacement of the RS-T segment is observed, the voltage of the negative T wave decreases, and S disappears. In the control intracavity pattern, QRS is mainly negative and there is a slight positive deviation of RS-T, probably caused by pressure of the exploring electrode on the subendocardial muscle; there is no negative T wave. After the ligation, the positive RS-T deviation decreases and a negative T wave of 3 mm. is recorded. The intracavity tracing does not change in other characteristics. We suppose that in this experiment the exploring intracavity electrode was wrongly oriented with relation to the infarct, and because of this the deviation was not registered.

2. In a majority of the cases, the changes were amazing; they were characterized by a positive displacement of RS-T in the intracavity pattern and depres-

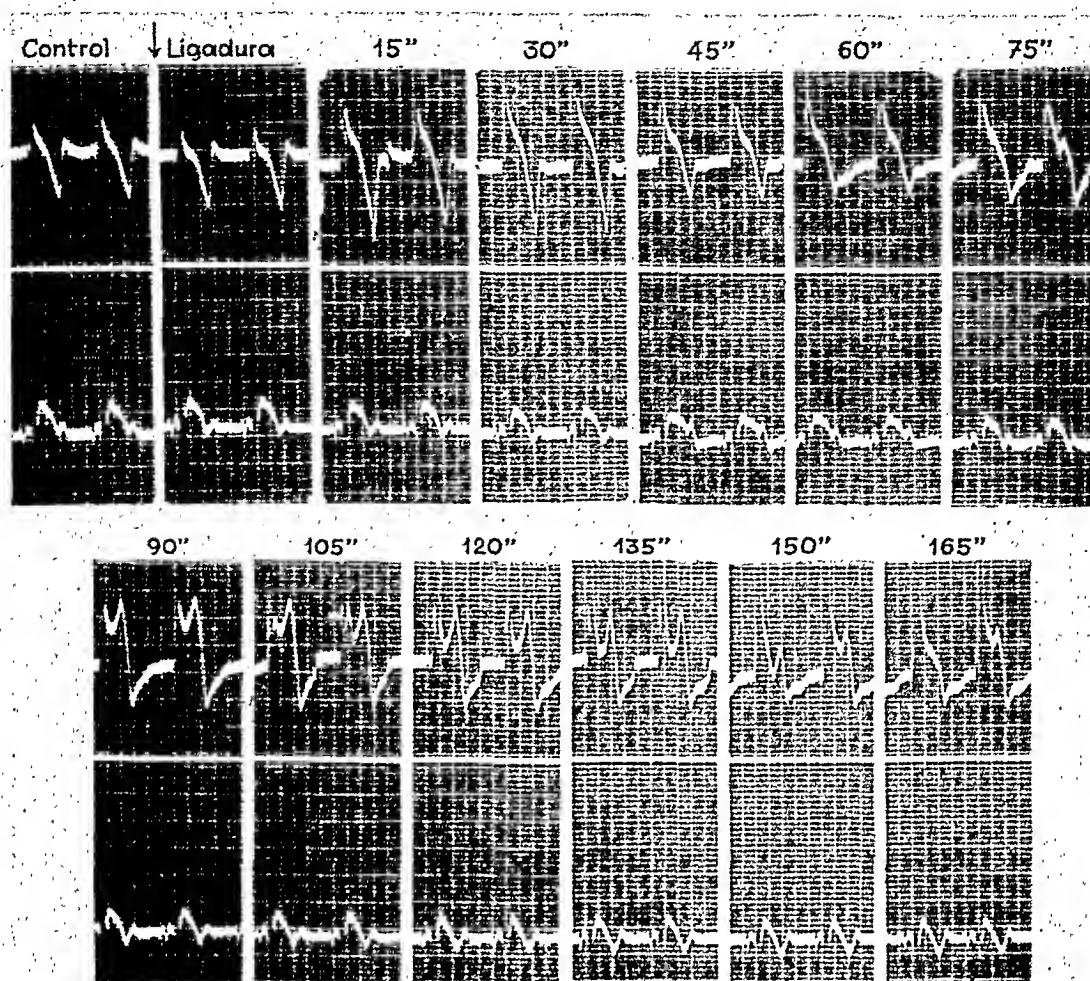


Fig. 2.—Unipolar tracings taken before and after the ligation of the left circumflex artery. The epicardial tracings (upper row) were taken from the site where the infarction was expected to appear and show the characteristic changes of an infarct: T wave waxing, positive RS-T displacement, and T wave waning. The intracavity tracings (lower row) show a positive displacement of the RS-T segment on the control; thereafter the RS-T displacement diminishes and the T wave becomes negative.

sion in the epicardial pattern (Figs. 3 and 4). The axis of injury in this type of infarct has a direction opposite to that determined by the ligation of the anterior descending artery, from which we infer that in dogs the left circumflex artery is more extensive in the subendocardial muscle than in the subepicardial.

In the upper records of Fig. 3, the exploring electrode was situated on the posterior surface of the heart. The lower records are intraventricular. The control was registered an hour and one-half after the ligation of the anterior descending artery. Afterward, at the moment indicated by the arrow, the left circumflex artery was also occluded. The time registered in the upper parts of the records indicates the moment at which the patterns were obtained after the occlusion of the circumflex artery. The cavity patterns after the second ligation show positive displacement of the RS-T, coincident with a negative shift of the epicardial pattern (at 55"). Later, the epicardial patterns have the shape of left bundle branch block; however, it is very improbable that this type of block exists because the intracavity potential is not of the RS type. The deflections become more and more bizarre until ventricular fibrillation appears.

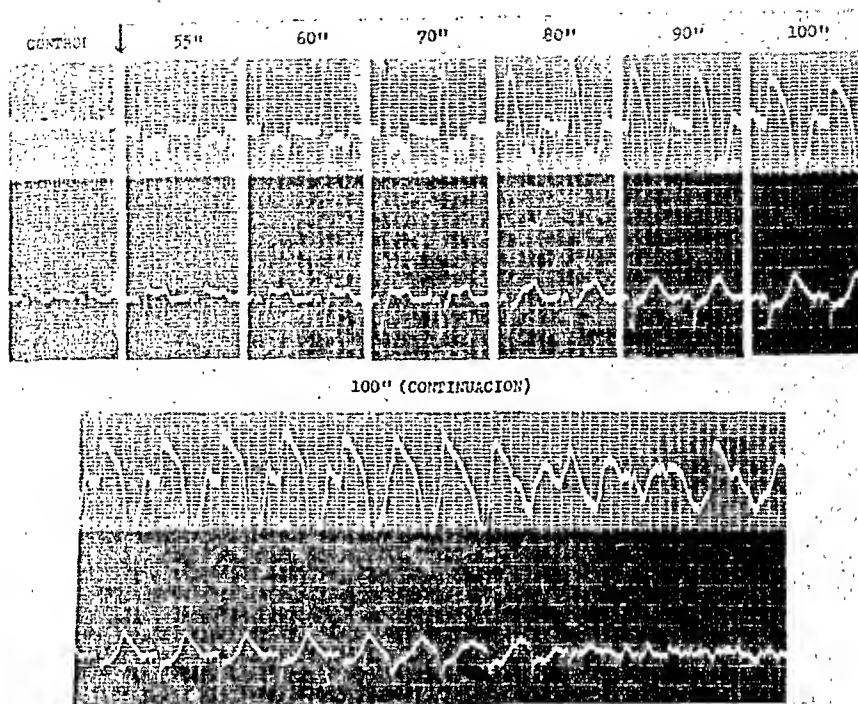


Fig. 3.—Unipolar tracings taken from the posterior surface of the heart (upper row) and from the left ventricular cavity (lower row). Control after ligation of the anterior descending artery. After the control tracing was made, the left circumflex artery was also ligated. Notice the positive displacement of the RS-T segment in the intracavity leads, coincident with negative displacement in the epicardial leads. After 70'', both tracings show changes which become more and more accentuated until ventricular fibrillation appears.

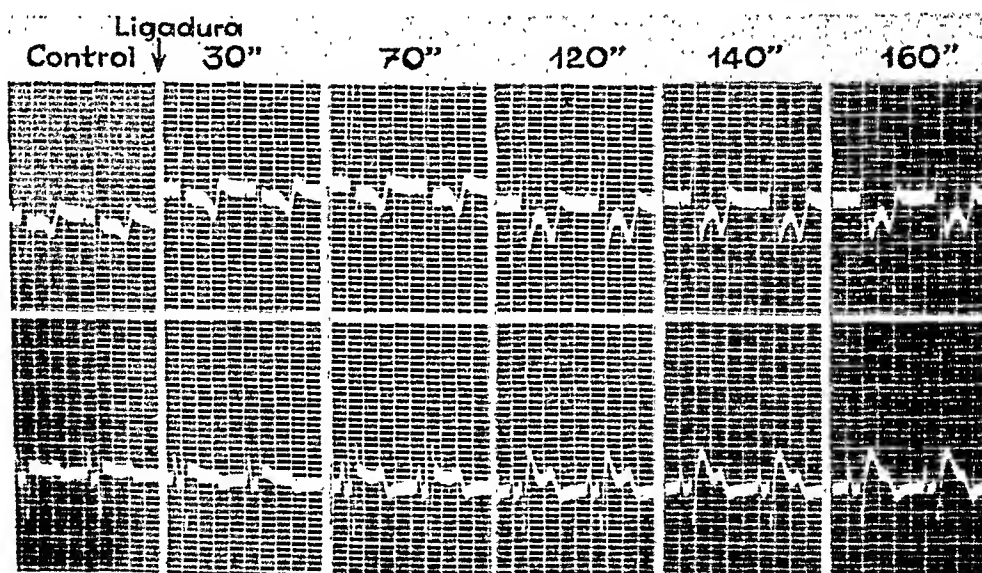


Fig. 4.—Unipolar tracings before and after the ligation of the left circumflex artery. The epicardial leads (upper row), taken from the posterior surface of the heart, show a deeper displacement of the RS-T segment. The left intraventricular leads (lower row) show a further positive displacement of the RS-T segment.

Right and Left Intraventricular Potentials During the Production of Ventricular Extrasystoles: After preparing a dog and introducing the exploring electrode into the left ventricular cavity, extrasystoles were produced by mechanical excitation at different points on the anterior surface of both ventricles. In Fig. 5 are sketched the points that were mechanically excited. Records 1, 3, 4, and 8 correspond to right ventricular extrasystoles; hence the excitation process spread

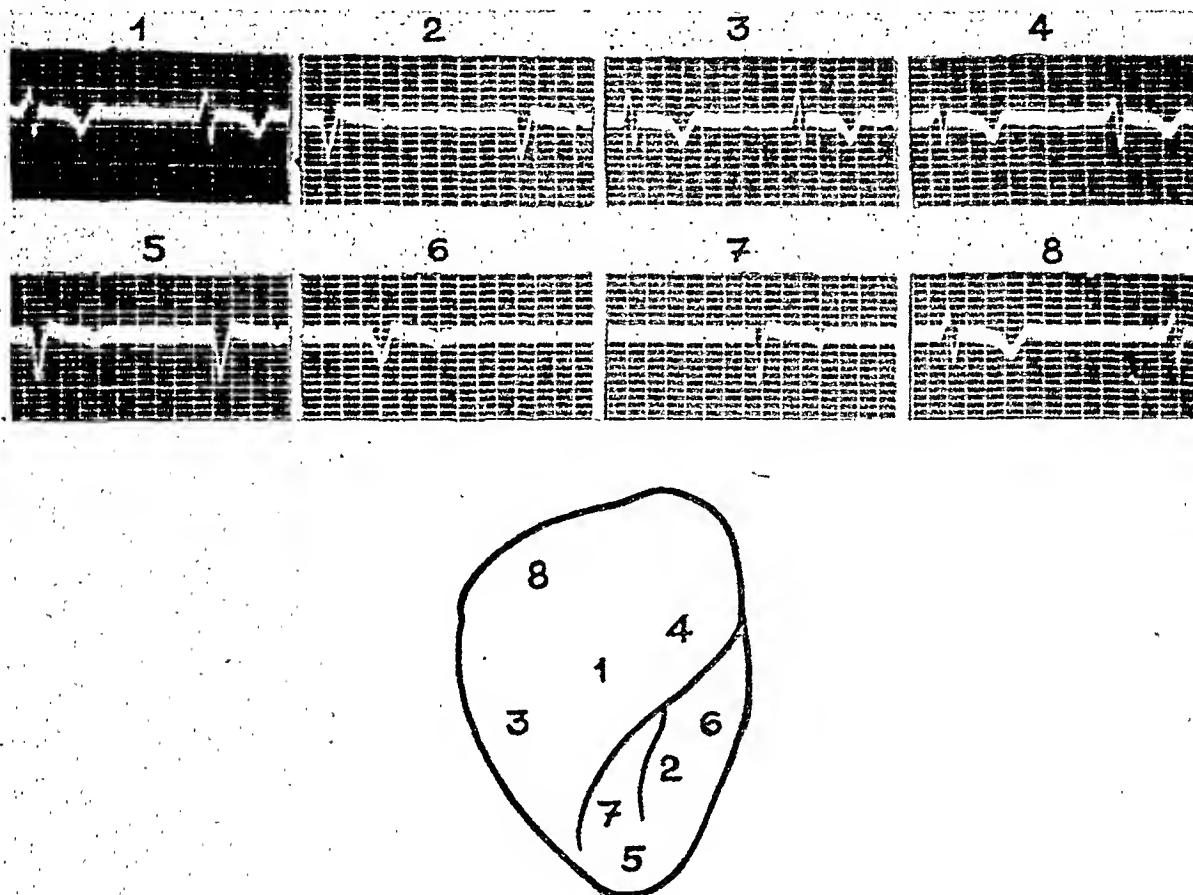


Fig. 5.—Unipolar leads from the left ventricular cavity, taken during mechanical excitation of the epicardial points indicated on the drawing. Whenever the right ventricle was stimulated, diphasic complexes of the RS type were obtained. The stimulation of the left ventricle produced a negative initial deflection.

from the right to the left heart and the QRS is of the RS type, first positive and afterward negative. The T wave is negative. The duration of QRS varied around 0.10 second. The records in Fig. 5, 2, 5, 6, and 7, correspond to left ventricular extrasystoles; here the excitation process spread from the left to the right heart, and therefore the QRS complexes are essentially negative without an initial positive phase. The T wave is slightly negative. The duration of the ventricular complex approximated 0.10 second.

In Fig. 6 the intracavity patterns correspond to the right ventricle. Whenever the excitation was produced in this ventricle, the intracavity curves were negative (lower curves of 1, 2, and 3); short crises of ventricular paroxysmal tachycardia were observed. When the excitation came from the left ventricle, the initial deflections of the extrasystolic intracavity curves was always positive. These results accord with a basic principle of the dipole theory, namely, that

the excitation wave conceived as a dipole determines a positive potential at the points which it approaches and a negative potential at the points from which it withdraws. The form of the pattern is the result of all the vectorial forces produced and depends mainly on the general direction of the excitation process and

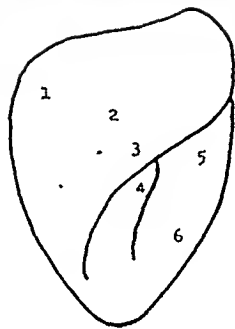
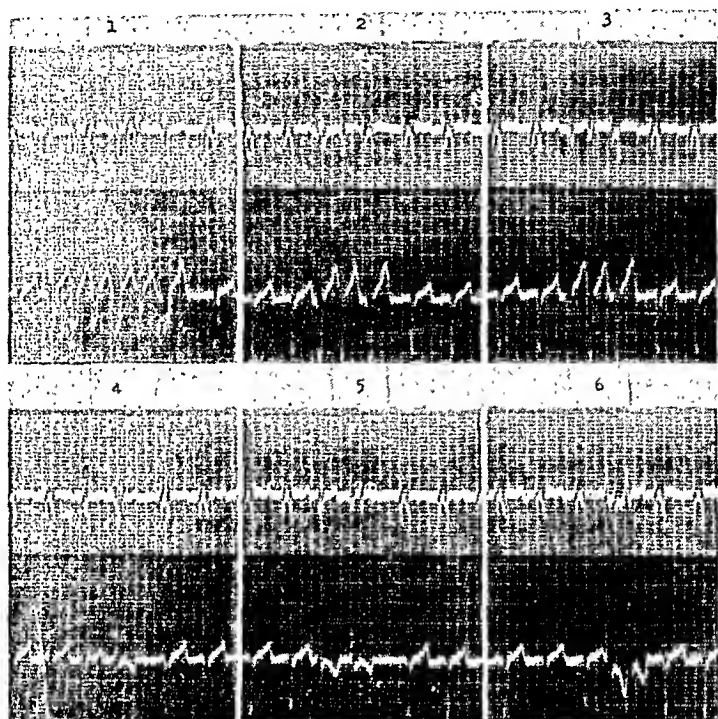


Fig. 6.—The pattern of ventricular extrasystole in the intracavitary leads. Unipolar epicardial leads, taken from the posterior surface of the heart (upper row), and unipolar right intraventricular leads (lower row). Whenever the right ventricle was stimulated (1, 2, and 3), the intracavity leads showed negative deflection. When the left ventricle was stimulated (4, 5, and 6) a positive initial deflection was obtained.

not on isolated forces originated at a given moment, as Nahum and Hoff⁹ claim. These authors, in failing to find any differences between the extrasystoles originating in the endocardium and those originating in the epicardium, differ from the opinions of Wilson and co-workers¹⁰ concerning the potential produced by the passing of the wave from the endocardium to the epicardium. Our experience, in general, supports the fundamental points proposed by Wilson, particularly with reference to the average of the excitation process.

Intracavity Potentials in Right Bundle Branch Block: Our results are very similar to those described by Wilson. After cutting the right branch of the bundle of His, the morphology of the right intracavity pattern is of the RS type (Fig. 7, 2, and Fig. 8). The production of block was tested by the morphology of Lead I

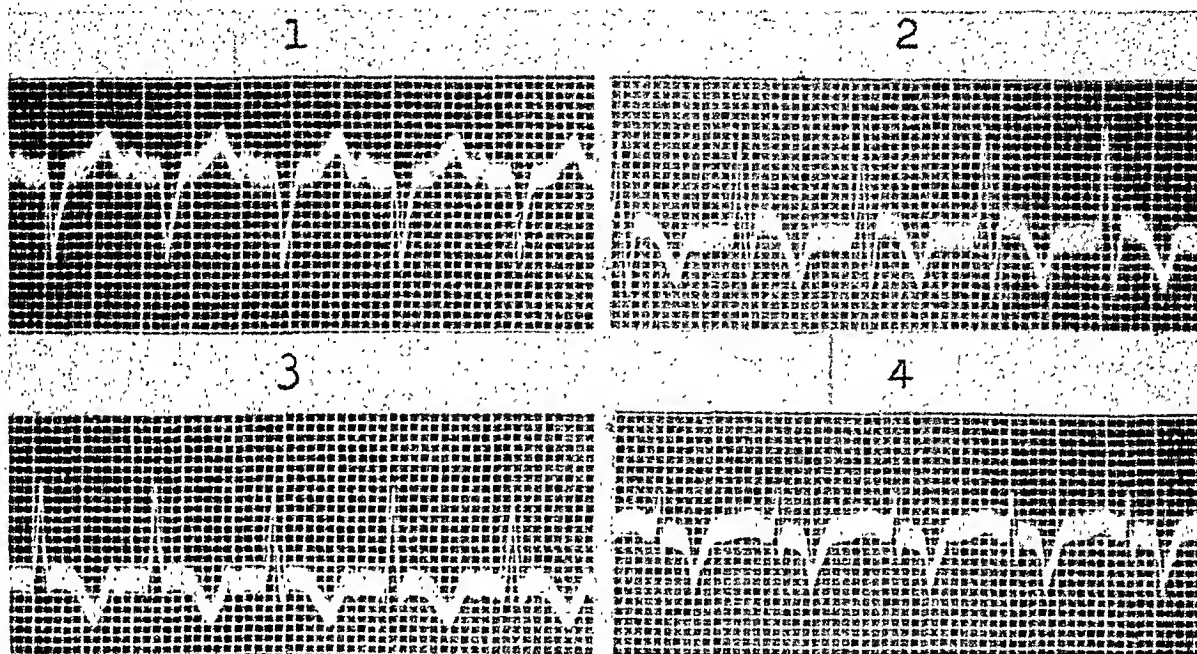


Fig. 7.—Different tracings after cutting the right bundle branch. 1, Lead I; 2, right intraventricular lead; 3, right intra-auricular lead; 4, left intra-auricular lead.

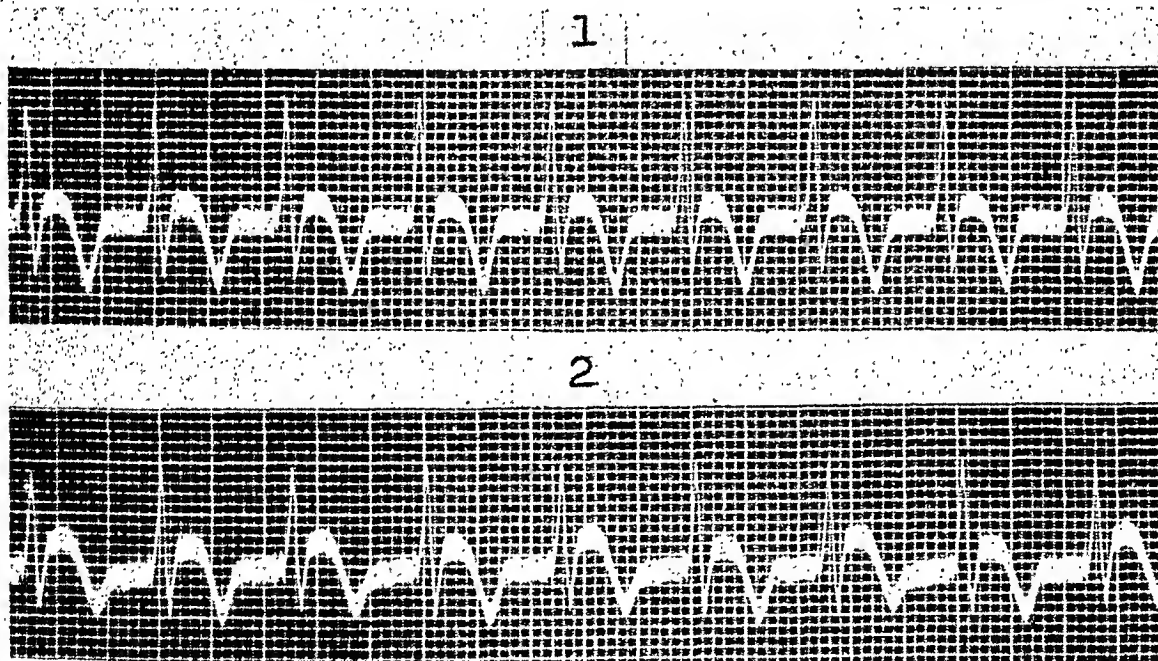


Fig. 8.—1, Right intraventricular lead after cutting the right bundle branch; 2, the same lead three minutes after the ligation of the anterior descending artery.

(Fig. 7, 1) and by the patterns registered over the epicardial surface of both ventricles (Fig. 9). All the records from the right ventricle show high R waves, delayed intrinsic deflections, and negative T waves. In the tracings obtained

from the left ventricle, the R waves are small, their peaks appear early, and the T waves are not negative. In our patterns some of the assertions of Wilson are mathematically corroborated, such as the opposition between the direction of the T wave and the larger surface of QRS and the value of the intrinsic deflection.

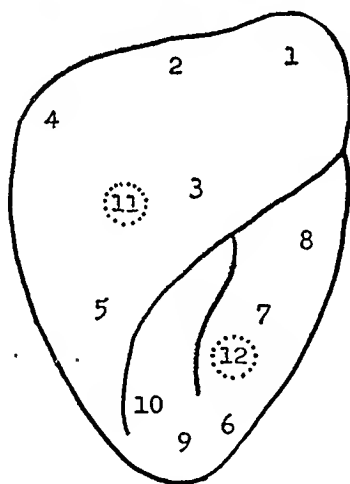
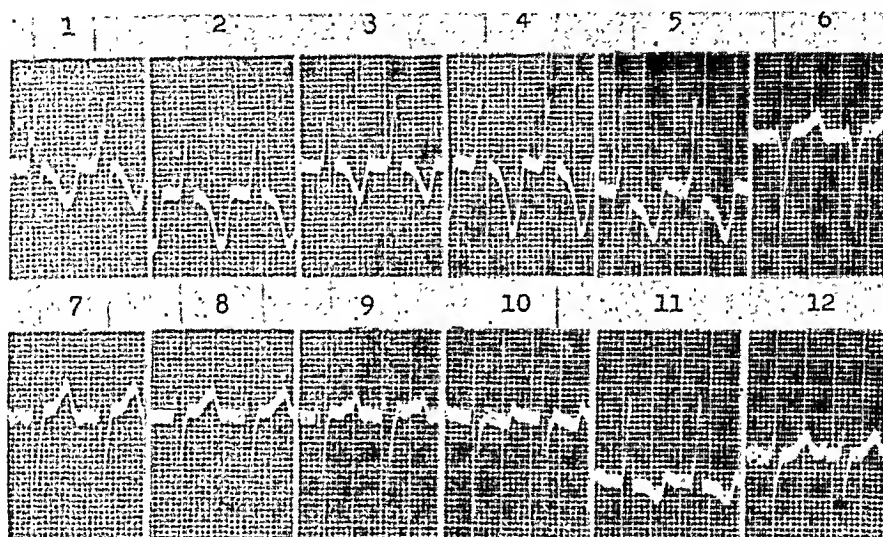


Fig. 9.—Unipolar leads taken from the epicardial surface after cutting the right bundle branch. Tracings taken from different points as indicated by the drawing. The two last points are from the posterior aspect of the heart.

Right intraventricular tracings obtained in cases of right bundle branch block are strikingly similar to those obtained in the same ventricle in cases of left ventricular extrasystoles. Both are of the RS type with negative T waves.

The right intra-auricular tracings in right bundle branch block show a ventricular complex of the QRs type with negative T waves (Fig. 7, 3, and Fig. 10, 1) and resemble left intra-auricular tracings associated with left bundle branch block (Fig. 14, 4). The normal intra-auricular tracing is of the QR type, with a large Q and small R wave (Fig. 14, 3).

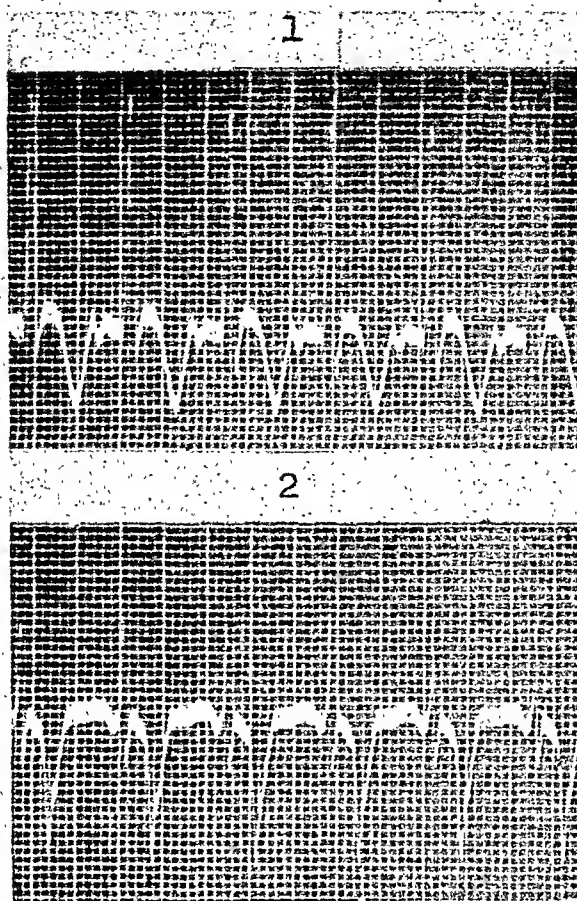


Fig. 10.—1, Right intra-auricular potential after severing the right bundle branch; 2, left intra-auricular potential in the same condition.

Intracavity Potentials in Left Bundle Branch Block: When the block is produced the left intraventricular control potential, which is negative (Fig. 11, 2), assumes an RS configuration (Fig. 11, 4) with a form similar to that found in tracings made from the right ventricular cavity when right bundle branch block is present, and from the left ventricular cavity when right ventricular extra systoles are present (compare Fig. 11, 4, with Fig. 5, 1, 3, 4, and 8 and with Fig. 8). In our left intraventricular pattern of left bundle branch block the T wave is negative. The right intracavity potential is not modified in its general form but may show slurrings (Fig. 12, 3). In this tracing the T wave becomes positive. The most favorable lead in which to verify the production of block is Lead I (Fig. 11, 3, Fig. 12, 2, and Fig. 14, 2).

In one of the experiments (Fig. 13), incomplete A-V block, 6 to 1, was produced, with left bundle branch block. The intraventricular potential shows the characteristic form (RS) of this type of block. Lead I is also characteristic.

In Fig. 14 the intra-auricular potentials are shown before and after cutting the left branch of the bundle of His. The left intra-auricular control tracing (Fig. 14, upper tracing of 3) shows an essentially positive P wave with a QRS complex of the QR type with a small, positive T wave. After the branch is cut, the P wave remains unchanged and the QRS complex turns into the qRs type with a negative T wave (Fig. 14, upper tracing of 4). The right intra-auricular control tracing (Fig. 14, lower tracing of 3) shows an essentially negative P wave

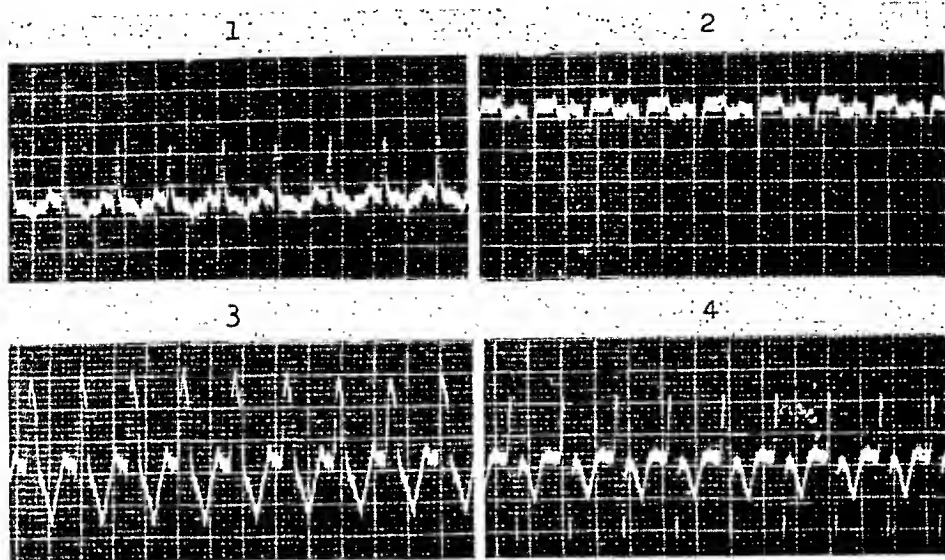


Fig. 11.—Experimental left bundle branch block. 1, Lead I, control; 2, left intraventricular potential, control; 3, Lead I after cutting the left bundle branch; 4, left intraventricular potential after cutting the left bundle branch.

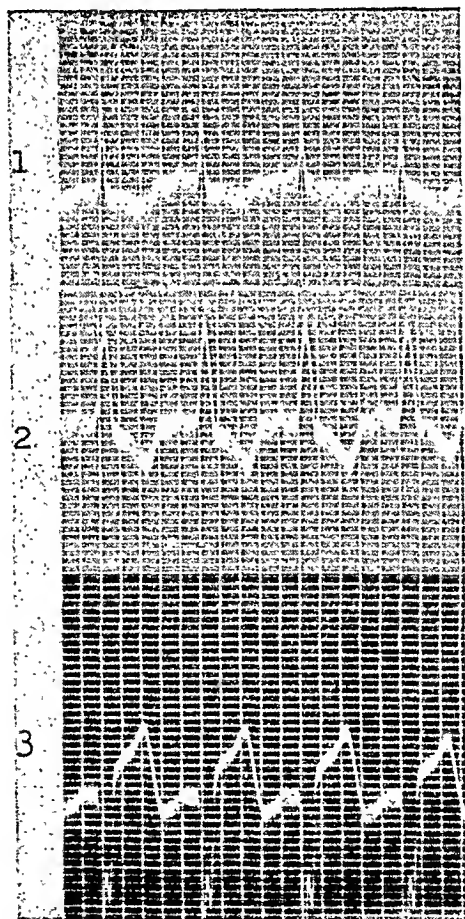


Fig. 12.—Experimental bundle branch block. 1, Lead I, control; 2, Lead I after cutting the branch; 3, right intraventricular potential after cutting the left bundle branch.

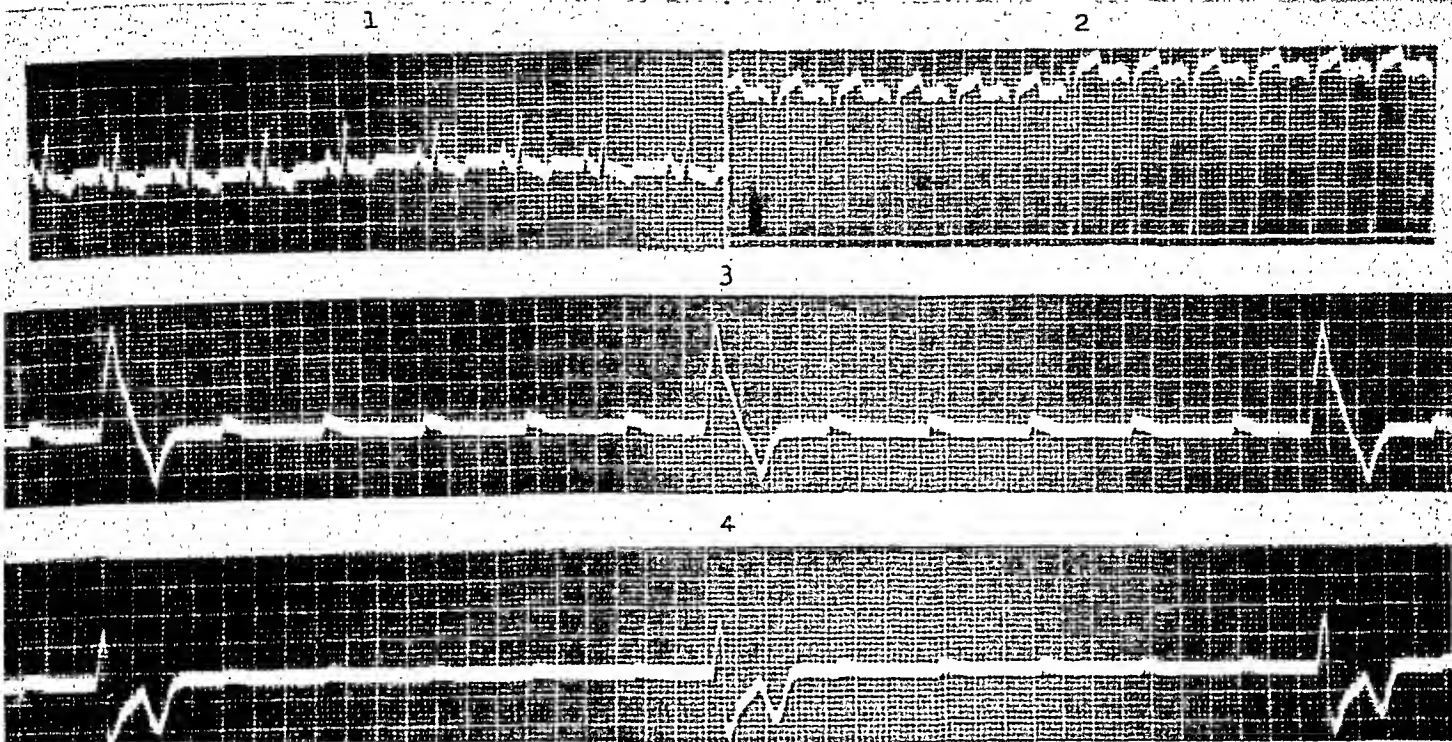


Fig. 13.—1, Lead I, control; 2, left intraventricular lead, control; 3, Lead I showing incomplete A-V block (6 to 1) and left bundle branch block; 4, left intraventricular potential showing the same changes.

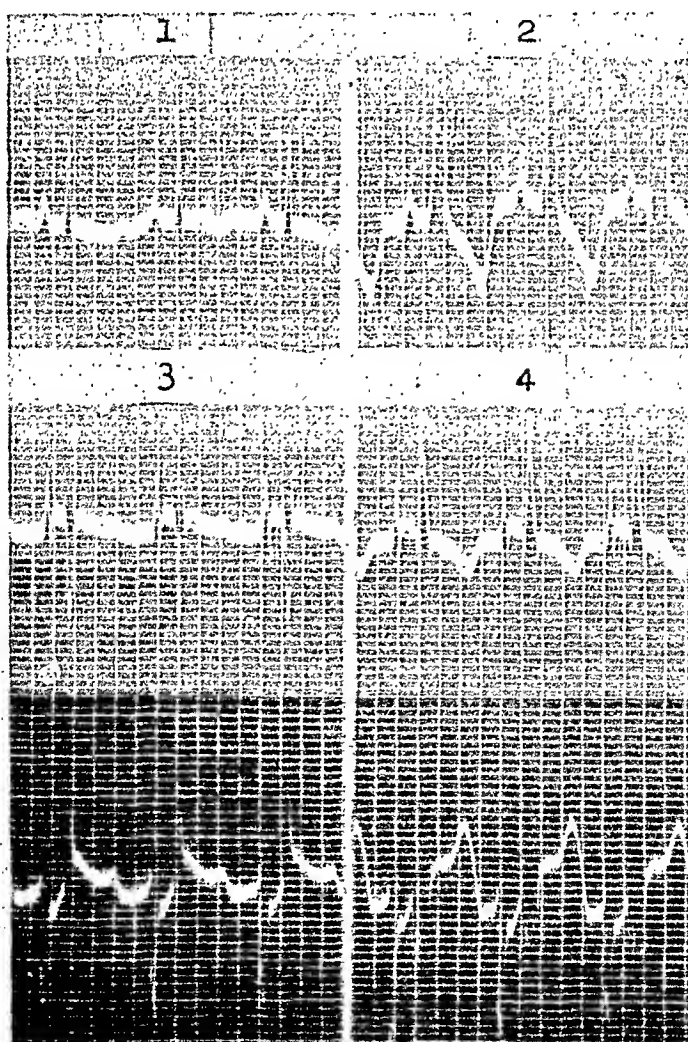


Fig. 14.—1, Lead I, control; 2, Lead I after cutting the left bundle branch; 3, left intra-auricular potential (upper tracing) and right intra-auricular potential (lower tracing), control; 4, the same leads after cutting the left bundle branch.

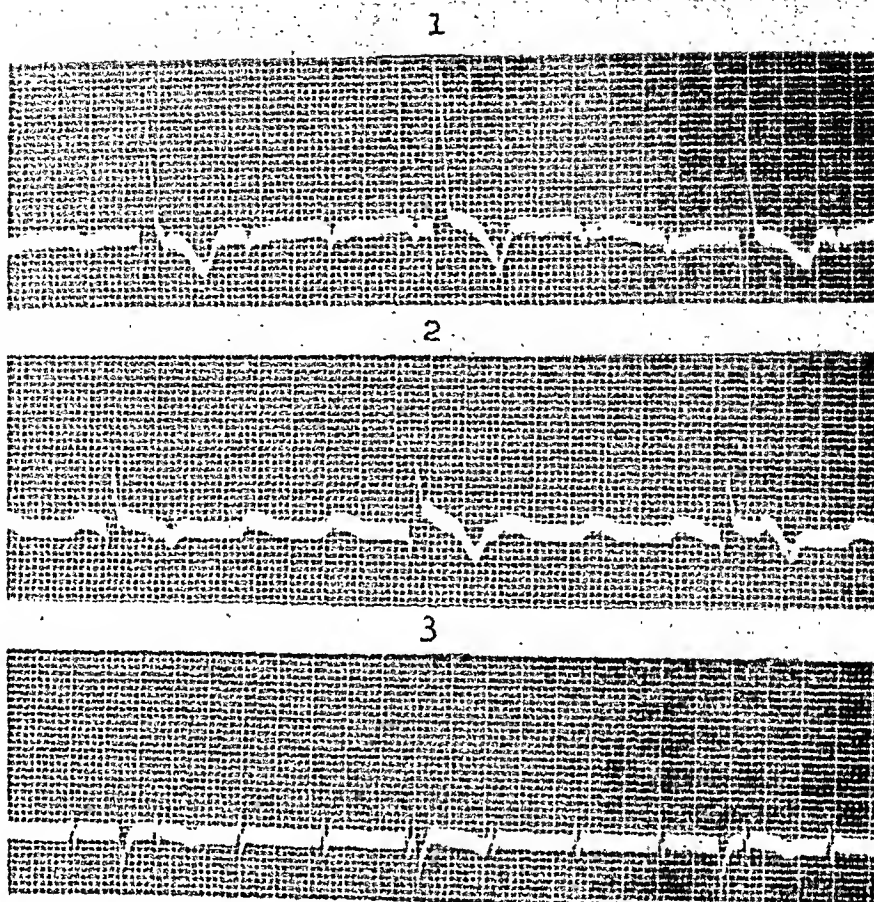


Fig. 15.—The effect of cutting both branches of the bundle of His. 1, Lead I; 2, right intraventricular potential; 3, left intraventricular potential.

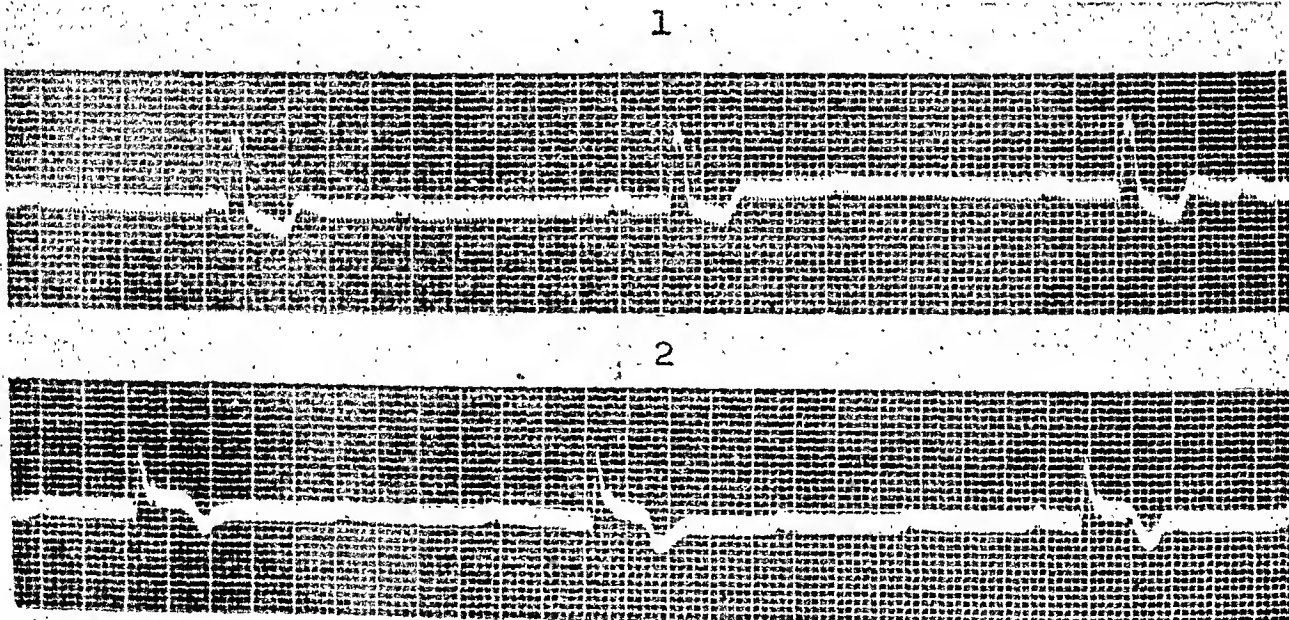


Fig. 16.—Complete A-V block with idioventricular rhythm simulating a left bundle branch block, after cutting the bundle of His. 1, Lead I; 2, left intraventricular lead.

with a ventricular complex of the QR type; when the branch is cut, the P wave remains unchanged and the ventricular complex becomes the QS type with notchings. In this tracing the T wave increases its positive potential (Fig. 14, lower tracing of 4).

Intraventricular Potentials in Cases of A-V Block: With A-V block and an idioventricular rhythm, the shape of the pattern is variable and depends on the site at which the ventricular stimulus originates. Thus in Fig. 15, the form of the right intraventricular pattern is of the QR type and that of the left ventricle is exclusively negative (QS), which suggests that the ectopic rhythm begins in the left ventricle. It is possible to confuse Lead I of Fig. 16 with left bundle branch block, but the two are differentiated by the facts that a Q wave is present in Lead I and that the QRS complex in the left intraventricular pattern is of the QR type and not the RS type which results from cutting the left branch.

THE RIGHT INTRACAVITY POTENTIAL OF THE HUMAN HEART

Six normal subjects and twenty patients with heart disease were studied. The exploring electrode was like that used in the animal experiments and was introduced through the right (less frequently through the left) external jugular vein. After local application of novocain, the vein was isolated. The introduction of the electrode was controlled by fluoroscopy. The indifferent electrode was attached to any one of the limbs. In almost every case the standardization of the galvanometer was such that 1 mv. produced a deflection of 2 millimeters. All patients received a small dose of barbiturate. In one case it was necessary to give intravenous ouabain because of paroxysmal dyspnea. In another case, the presence of the electrode in the ventricular cavity brought on chest pain that disappeared shortly after the electrode was retracted. Still another patient complained of a vague pain in the back of the chest and right shoulder, coincident with the recording of a monophasic wave, while the catheter was in contact with the ventricular endocardium. When the catheter was retracted, the patient presented a short run of ventricular extrasystoles and the monophasic wave disappeared. Every patient received a prophylactic treatment of penicillin for two days after the operation and follow-up was continued for one month afterward. None of the patients showed any lasting ill effects.

The Normal Electrocardiogram of the Intracavity Leads.—

P Wave: The shape of the P wave is variable, depending upon the position of the exploring electrode. When this is in the superior vena cava or near the sinus node, the P wave (Figs. 17 and 18) is exclusively negative (PQS according to Hecht's terminology). Its amplitude is greater when the electrode is near the sinus node than when it is in the vena cava.

When the electrode is in the center of the auricle, the P wave is diphasic (Fig. 19, C) of the plus-minus type (PRS). The preponderance of the positive or negative phase depends upon the distance of the exploring electrode from the sinus node. Sometimes the P wave has a small initial negativity (PQRS), which could be attributed to irregular distribution of the wave of excitation leaving the

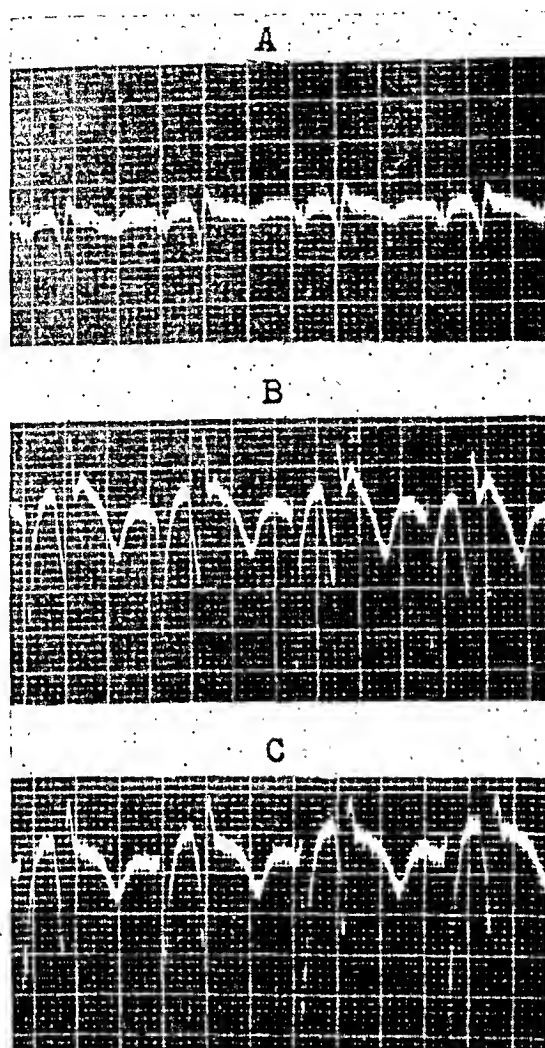


Fig. 17.—Normal intracavity potential. A, Superior vena cava; B and C, high auricular level.

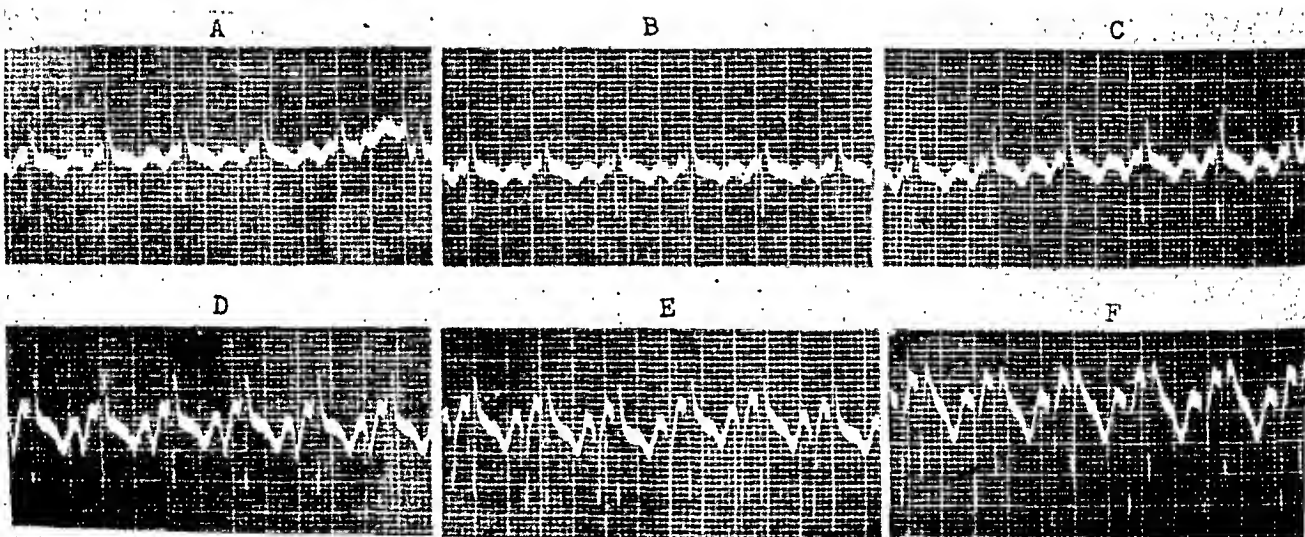


Fig. 18.—Normal intracavity potential. Unipolar tracings from: A, B, C, and D, superior vena cava, at different levels; E and F, high auricular level.

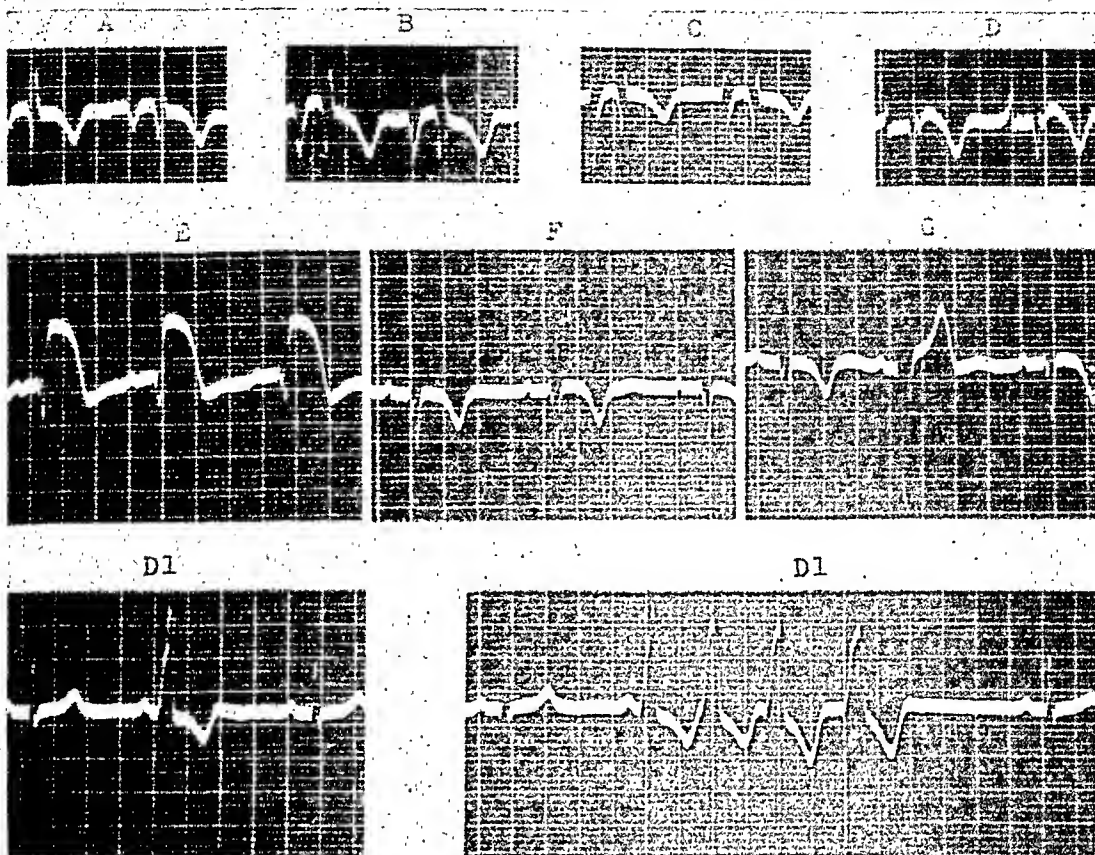


Fig. 19.—Right ventricular extrasystoles. Unipolar tracings from: A, superior vena cava; B, high auricular level near the sinus; C, mid-auricular level; D, E, F, and G, ventricular cavity.

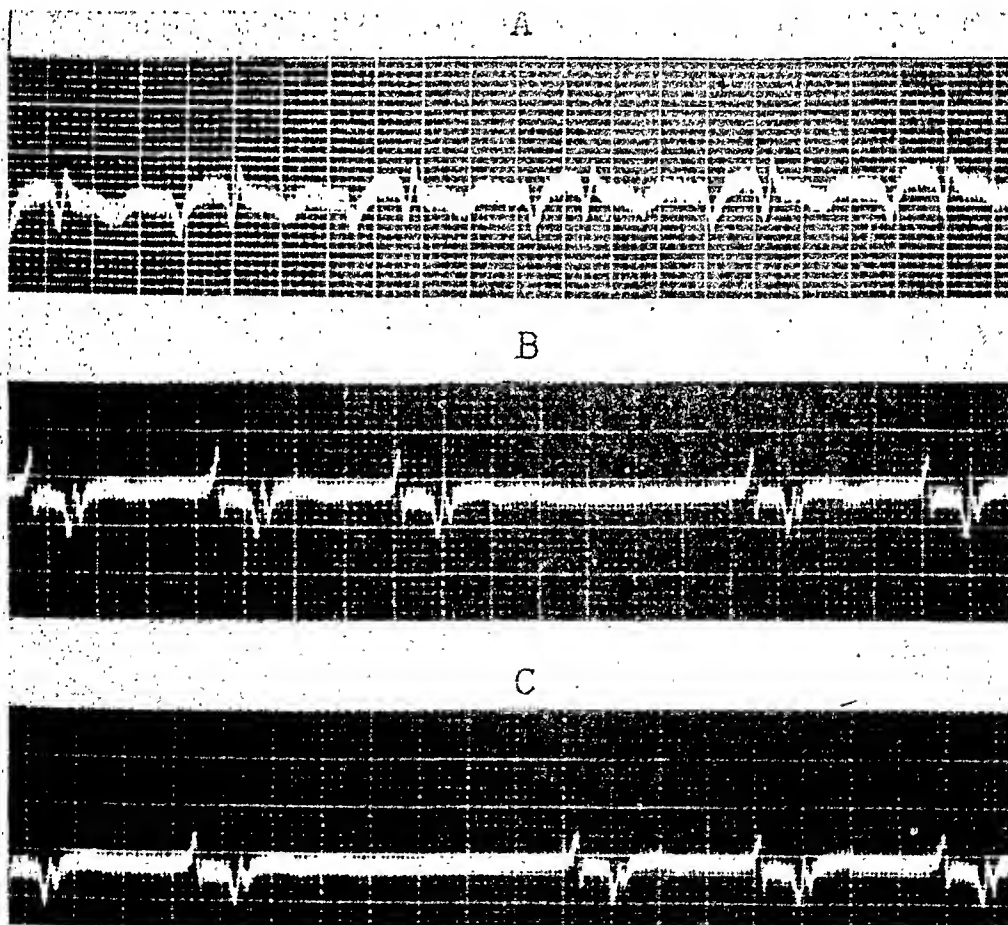


Fig. 20.—Sinoauricular block. Unipolar tracings from: A, high auricular level, near the sinus node; B and C, low auricular level.

sinus node, resulting, at a given moment, in predominance of the forces leaving the exploring electrode (Fig. 22, *B*).

When the electrode is in the lower part of the auricle, the P wave is exclusively positive or diphasic (Fig. 20, *B* and *C*) with a definite preponderance of the positive phase (PRs). In the inferior vena cava or the right ventricular cavity, the P wave is exclusively positive and of lower voltage. In a few instances when the electrode is in the inferior vena cava, the P waves are of high voltage (Fig. 24, *E* and *F*).

The shape of the auricular wave is in accordance with a principle of the dipole theory: when the wave of excitation approaches a point, this point becomes positive; when it leaves a point, this point becomes negative.

If the pacemaker is not in the sinus node but in the A-V node, the auricular potentials become reversed; that is, positive at the level of the sinus and negative at the level of the A-V node. Fig. 21 shows a shifting of the pacemaker from the sinus to the A-V node which resulted in a shortening of the P-R interval from 0.15 to 0.10 second. The exploring electrode at the level of the sinus detected a negative P wave when the P-R interval was 0.15 second, and a positive P wave when it was 0.10 second; the ventricular complex was slightly modified.

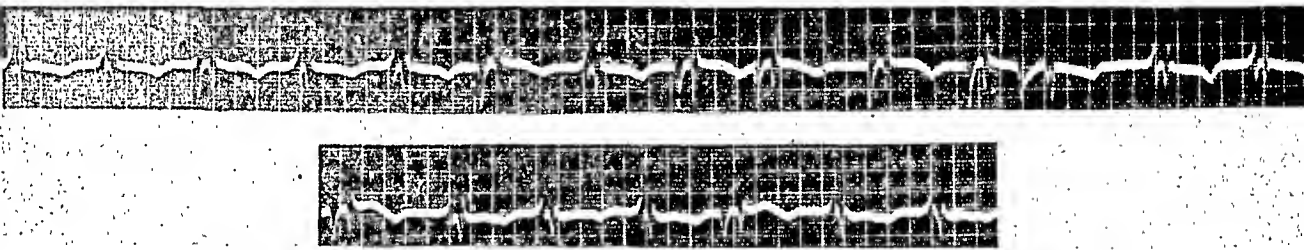


Fig. 21.—Wandering pacemaker. Continuous tracing from a high auricular level, near the sinus node. The negative P wave (during sinus rhythm) becomes positive when the pacemaker shifts to the A-V node.

Ventricular Complex: The ventricular complexes taken from the auricular cavity are always predominantly negative, and may be of the QR, QRS, rSR' or RS type (Figs. 17, 18, 19, 20, 21, and 35). At high and middle auricular levels, the two first types, QR and QRS, are more frequent; at lower auricular levels and near the septum, the two latter types, rSR' and RS, are more common. We speak of a "late R" when the ventricular complex is of the QR or QRS type and of an "early R" when the complex is of the RS type; when the complex is of the rSR' type, we call the first positive wave "early R" and the second positive wave "late R."

In the experiments in animals we found that the voltage of the late R in the right auricular cavity was modified by section of any of the branches of the bundle of His. The voltage increased when the right branch was cut, and the late R disappeared when the left branch was cut. For this reason we assume that the late R is due to late activation of certain portions of the right ventricle.

The early R obtained at lower auricular levels is attributed by us to septal activation. No such wave is found at the upper levels, probably because the

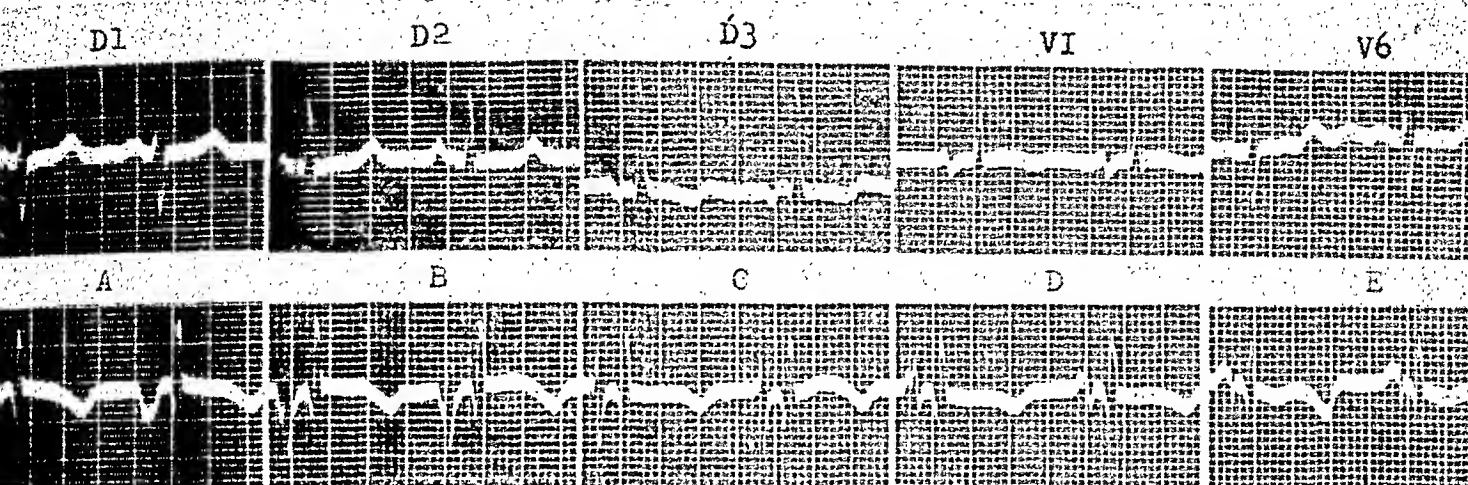


Fig. 22.—Right ventricular hypertrophy. Unipolar tracings from: A, high auricular level near the sinus node; B, high auricular level near the mid-auricle; C, mid-auricular level; D and E, low auricular levels.

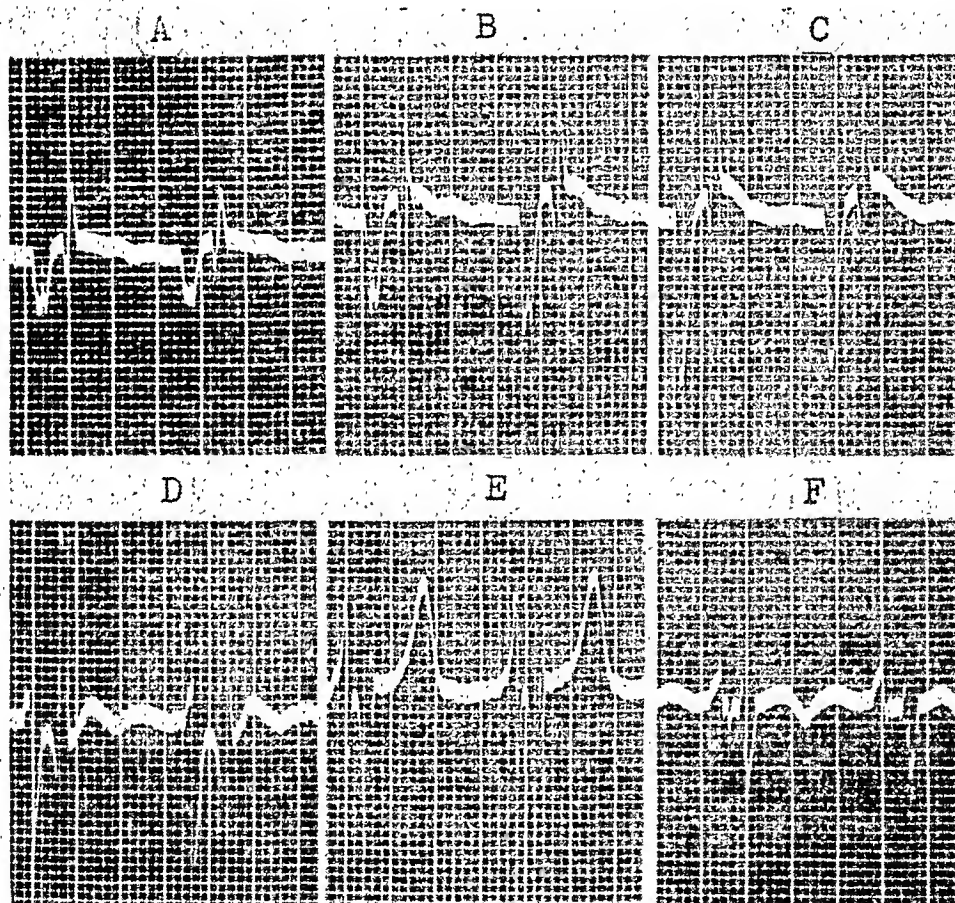


Fig. 23.—Right ventricular hypertrophy. Unipolar tracings from: A, superior vena cava; B and C, auricular cavity near the sinus node; D, high auricular level; E, mid-auricular level; F, low auricular level.

exploring electrode lies in a perpendicular line with the vector which indicates the activation of the ventricular septum.

The negative deflections of the ventricular complexes found in the auricular cavity are probably due to activation of the free walls of both ventricles.

In the right ventricular cavity the ventricular complex is commonly of the RS type. We attribute the R wave to septal activation and the S wave to activation of the free walls of both ventricles (Fig. 19, *F* and *G*; Fig. 32, *A*; Fig. 33, *D*).

Right Ventricular Hypertrophy: The general form of the P wave is similar to that found in normal subjects, but these waves tend to be slurred and notched. The QRS complex in intra-auricular tracings is also similar but with different voltage of its deflections: negative components, Q and S, predominate over the R waves in the normal subjects and the R waves are greater than the Q and S waves in patients with hypertrophies. In other words, positive deflections predominate in right ventricular hypertrophy (Figs. 22, 23, and 24). It seems logical to assume that the high R wave of right ventricular hypertrophy is due to the late activation of some hypertrophied muscular portions of the right ventricle.

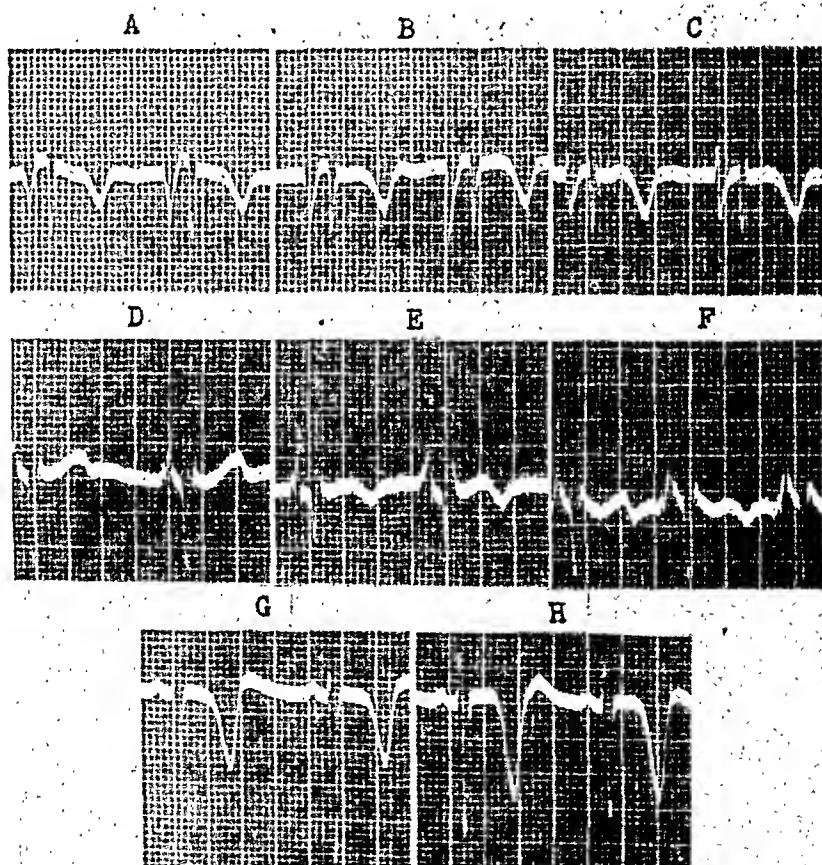


Fig. 24.—Right ventricular hypertrophy. Unipolar tracings from: A, superior vena cava; B, auricular cavity near the sinus node; C, mid-auricular level; D, low auricular level; E and F, inferior vena cava; G, ventricular cavity; H, same cavity near the pulmonary conus.

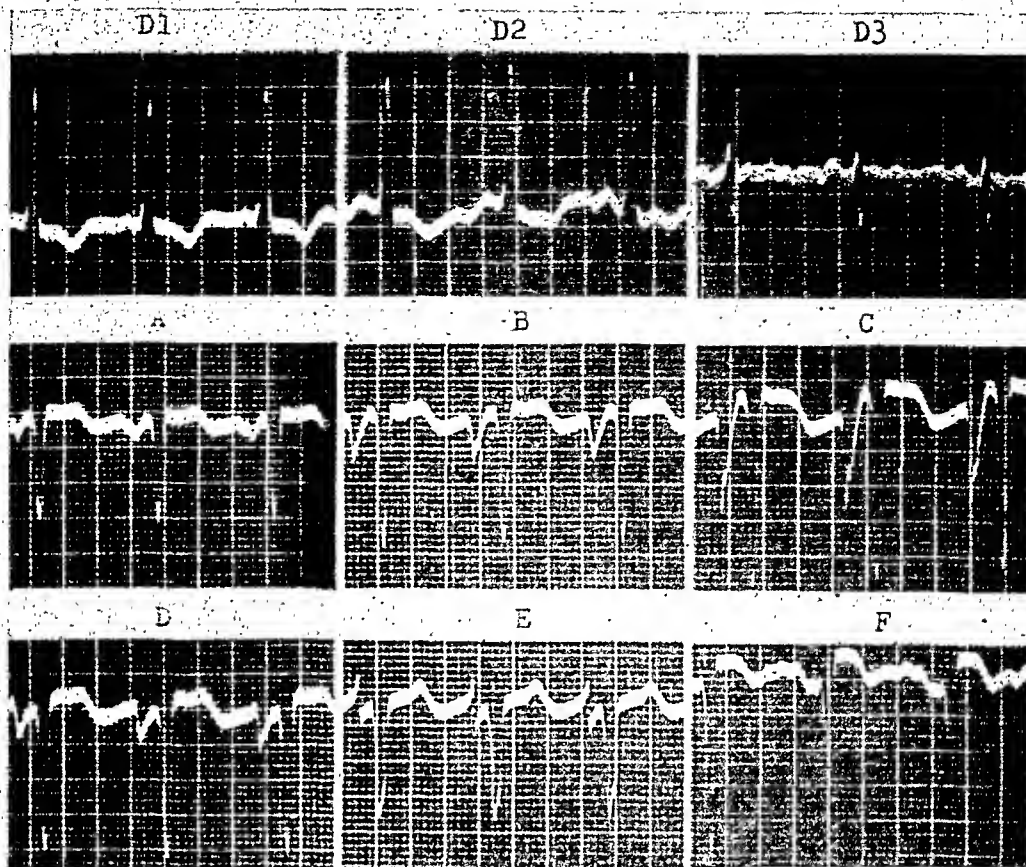


Fig. 25.—Left ventricular hypertrophy. Unipolar tracings from: A, superior vena cava; B, auricular cavity near the sinus node; C and D, high auricular level; E, low auricular level; F, ventricular cavity.

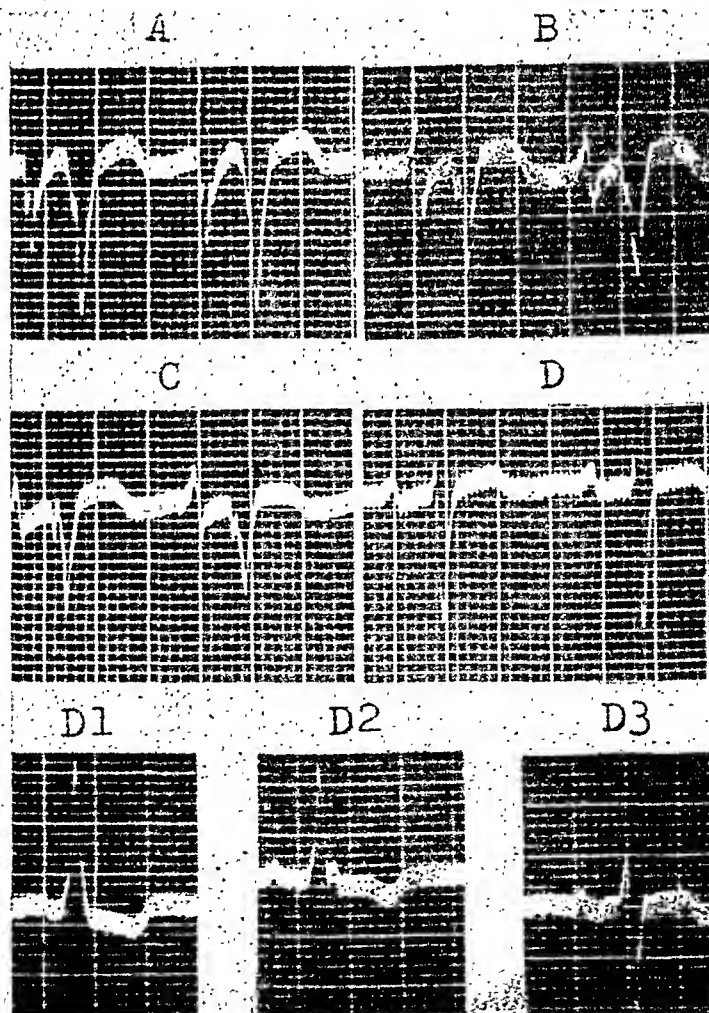


Fig. 26.—Left ventricular hypertrophy. Unipolar tracings from: A, auricular cavity near the sinus node; B, mid-auricular level; C, low auricular level; D, ventricular cavity.

In the right ventricular cavity, the tracing is similar to the normal: RS (Fig. 24, *G* and *H*). The first positive deflection which is small, appears early and may be attributed to septal activation. The negative deflection, which is larger, may be ascribed to the activation of the free walls of both ventricles.

In one patient with pulmonary emphysema and chronic cor pulmonale (Fig. 24, *H*) the catheter was introduced up to the pulmonary conus. There the early R was higher than in any other part of the right ventricle. This may be a normal finding or it may have been due to hypertrophy of the upper part of the septum.

Left Ventricular Hypertrophy: The P wave is similar to that found in normal subjects. The ventricular complexes are almost the same at any level in the auricle: of the QS or QRS type; that is, with negative deflections predominating (Fig. 25, *B*, *C*, *D*, and *E*; Fig. 26, *A*, *B*, and *C*; Fig. 27, *A*, *B*, and *C*).

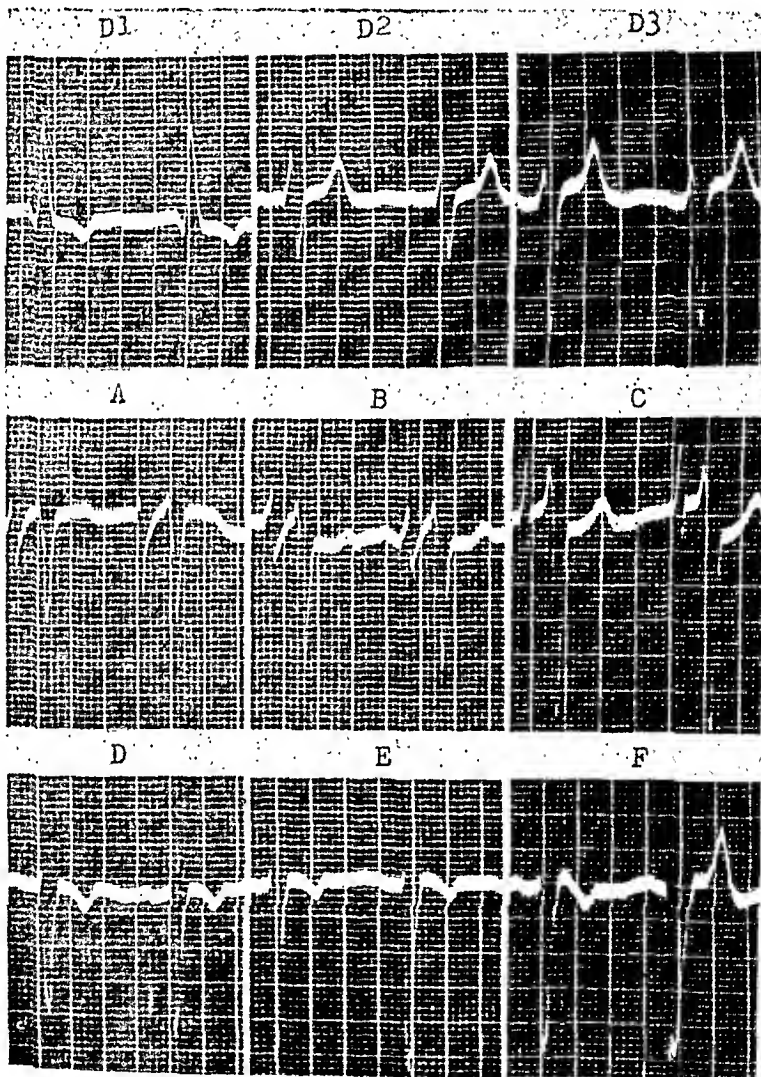


Fig. 27.—Left ventricular hypertrophy. Unipolar tracings from: *A*, high auricular level; *B*, mid-auricular level; *C*, low auricular level; *D*, *E*, and *F*, ventricular cavity.

The late R is either small or absent, probably because of the opposition of the forces of the hypertrophied walls of the left ventricle. This occurs also in left bundle branch block in animals and men. The intraventricular tracing was always of the rS type (Fig. 25, *F*; Fig. 26, *D*; Fig. 27, *D*, *E*, and *F*), generally with a positive T wave.

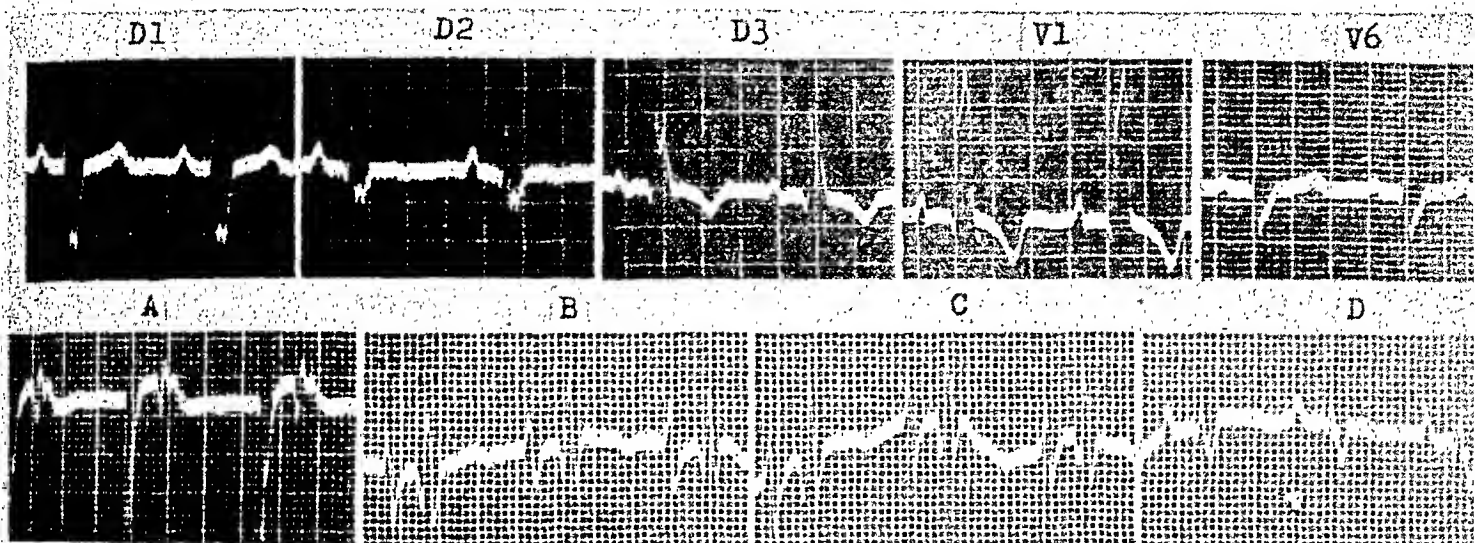


Fig. 28.—Right bundle branch block. Unipolar tracings from: A, high auricular level; B and C, mid-auricular level; D, inferior vena cava.

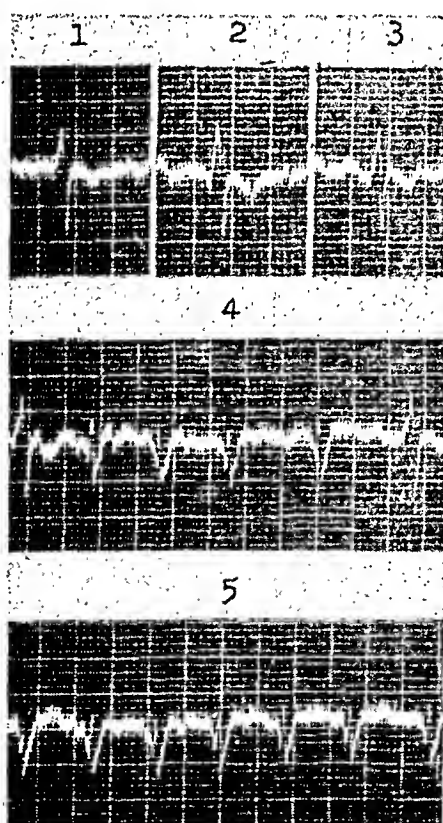


Fig. 29.—Unipolar right intraventricular leads in cases of right bundle branch block. Notice the typical plus-minus form of the QRS complex (1, 2, and 3) and the small run of right ventricular extrasystoles produced by the contact of the exploring electrode (4 and 5).

In one of our patients (Fig. 27, C) the early R was higher in the lower part of the auricle than in the right ventricle. This may be ascribed to hypertrophy and bulging of the upper part of the septum.

Right Bundle Branch Block: The intra-auricular QRS complexes are similar to those found in right ventricular hypertrophy, with a definite preponderance of positive deflections (Fig. 28, A, B, and C).

At the upper part of the auricle, the late R is broad and slurred (Fig. 28, A) like that found in Lead VR in the same condition. At the lower part of the auricle the late R is still predominant but less slurred (Fig. 28, B and C). The tracing is strikingly similar to that found in experimentally produced block in the dog. One case (Fig. 28) had the same shape in Lead V₆ and in the tracing obtained from the inferior vena cava.

The intraventricular tracing (Fig. 29, 1, 2, and 3) shows diphasic QRS complexes (of the RS type) with negative T waves and is more or less like the tracing obtained from the right ventricular cavity in experimentally produced right bundle branch block and left ventricular extrasystoles.

Left Bundle Branch Block: The P wave shows no changes. The QRS complex in tracings made with the electrode in the lower auricle presents purely negative (QS) deflections (Fig. 30, A, B, and C). In tracings made from the upper part of the auricle (Fig. 30, A) the complex is of the W type, but its ascending portion does not go above the isoelectric line; therefore, strictly speaking, they are QS complexes with splinterings.

It is important to remember that the normal auricular tracings in both man and the dog show a late R. In the dog this wave disappears when the left branch is severed; in man a late R is not found in left bundle branch block.

In tracings made from the ventricular cavity, there is a deep QS complex (Fig. 30, D and E), without the initial positivity described by Hecht.⁶ The auricular as well as the ventricular tracings present a positive T wave with positive displacement of the RS-T segment.

In Fig. 31 are shown the tracings obtained inside the cavities of the right heart in normal cases, in ventricular hypertrophy, and in two types of bundle branch block.

Ventricular Extrasystoles.—In several of the experiments, the mechanical action of the exploring electrode brought on premature ventricular beats (Figs. 19, 27, 29, and 32) or even short runs of ventricular paroxysmal tachycardia (Figs. 19 and 29). At times these premature beats could be produced at will. These beats evidently arose from the right ventricle. The intraventricular tracings always showed a QS complex while the first lead showed exclusively positive complexes. The T wave was always opposite in direction to the QRS deflection. The form of these tracings is very similar to that of experimentally produced right ventricular extrasystoles in animals and to that of left bundle branch block in both men and animals.

Miscellaneous Conditions.—Some other conditions were incidentally studied and are presented here.

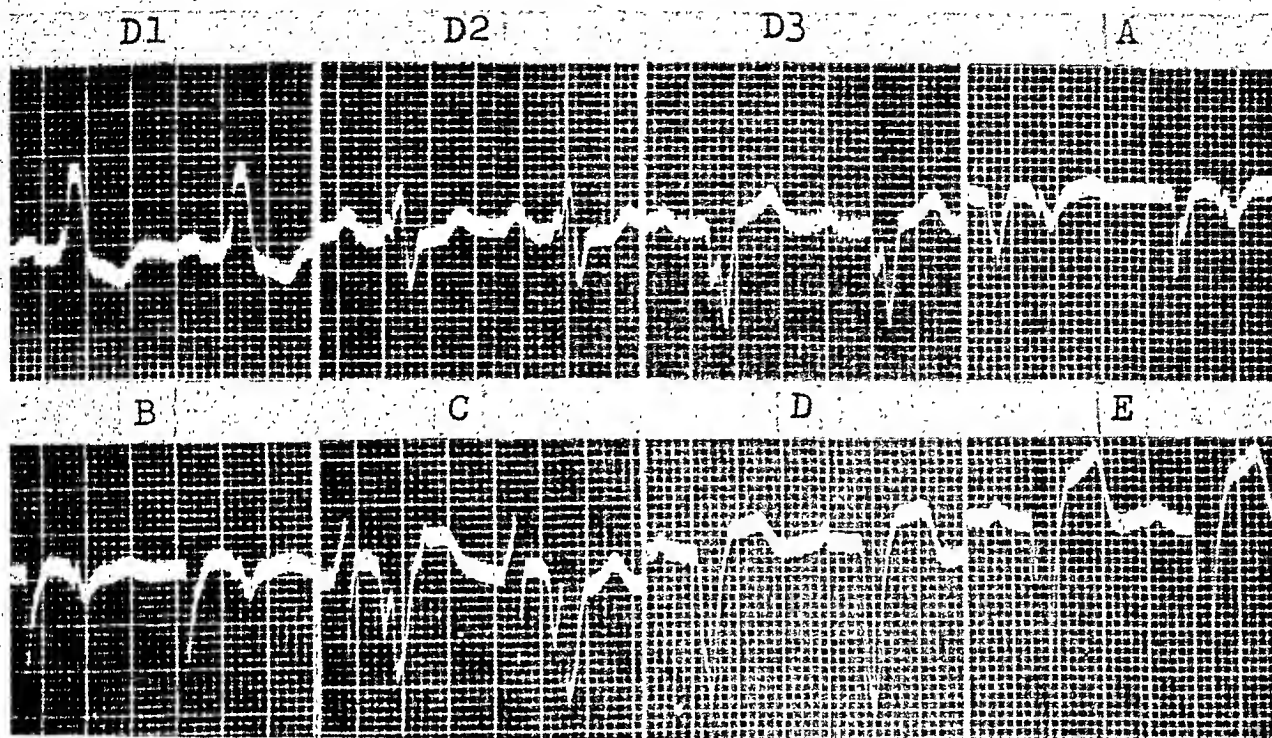


Fig. 30.—Left bundle branch block. Unipolar tracings from: A and B, high auricular levels near the sinus node; C, mid-auricular level; D and E, ventricular cavity.

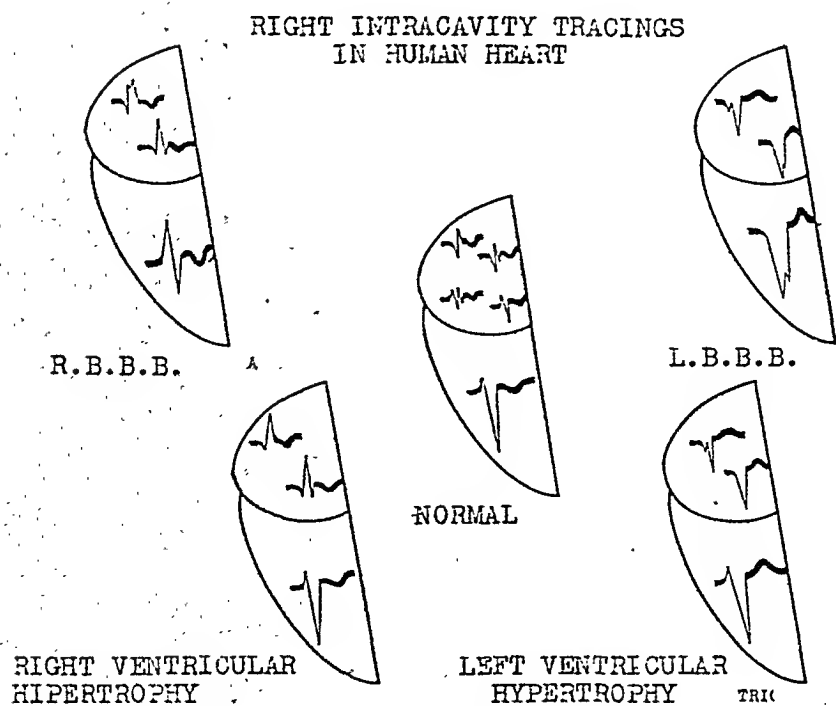


Fig. 31.—The right intra-auricular and intraventricular tracings in different conditions.

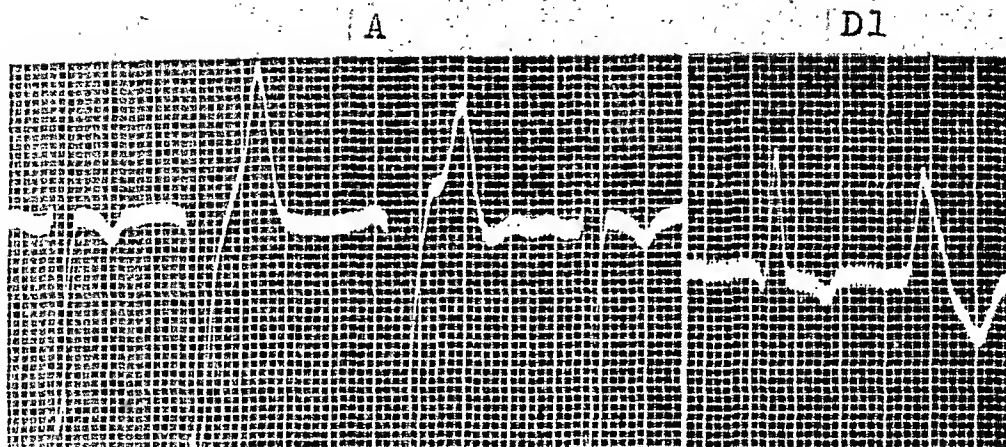


Fig. 32.—Right ventricular extrasystoles. A, right intraventricular tracing. Notice the negative (QS) complex and the positive T wave of the premature beats; B, in Lead I, the aspect of the premature beat is like that of left bundle branch block.

Subendocardial Ischemia (Fig. 33): One of our patients with clinical angina pectoris developed a squeezing chest pain radiating to the neck and left shoulder while the record was being taken. The T wave, which previously had a negative amplitude of -14 mm. (Fig. 33, E), became more negative with an amplitude of -22 to -25 mm. (Fig. 33, F). The R wave did not change. It is logical to assume that a subendocardial ischemia appeared or became accentuated.

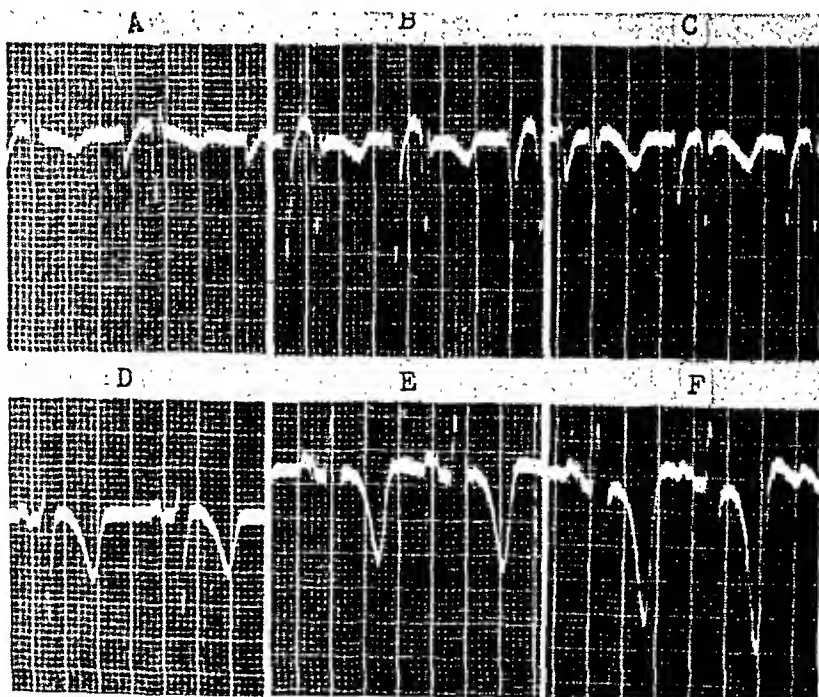


Fig. 33.—Subendocardial ischemia. Unipolar tracings from: A, superior vena cava; B, auricular cavity, near the sinus node; C, high auricular level; D and E, intraventricular tracings; F, the same as (E) after the appearance of a severe precordial pain; notice the waxing of the T wave.

Auricular Flutter: In one case with auricular flutter and probably complete A-V block we found (1) typical flutter waves with a rate of 300 per minute, (2) ventricular rate of 36 per minute, and (3) occasional cycles of ventricular escape (Fig. 34).

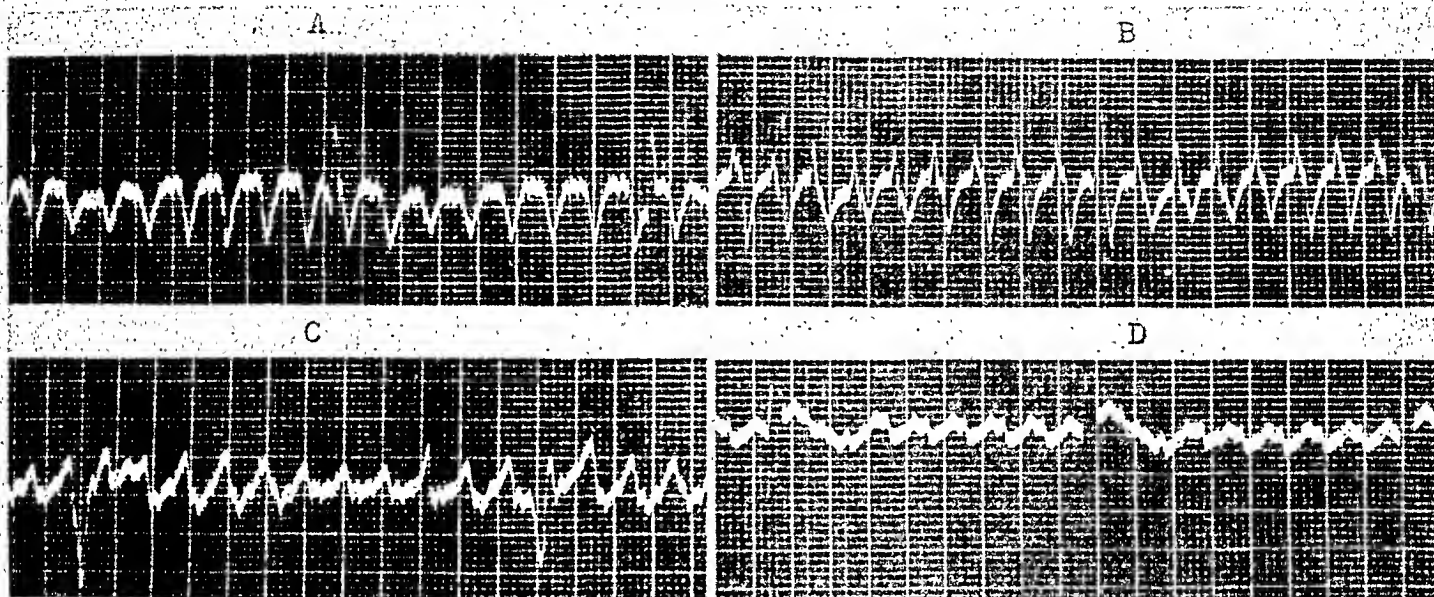


Fig. 34.—Auricular flutter. Unipolar tracings from: A, high auricular level; B, mid-auricular level; C, low auricular level; D, ventricular cavity.

At the upper auricular levels, the flutter waves were predominantly negative; at medium levels, they were diphasic and separated by a horizontal slurring which probably represents the isoelectric line; at lower levels, they were mainly positive. In tracings made from the ventricular cavity, the flutter waves were also positive but of less voltage. The ventricular complexes of this case suggest right ventricular hypertrophy.

Sinoauricular Block: Fig. 20 shows a case of sinoauricular block in a clinically normal subject.

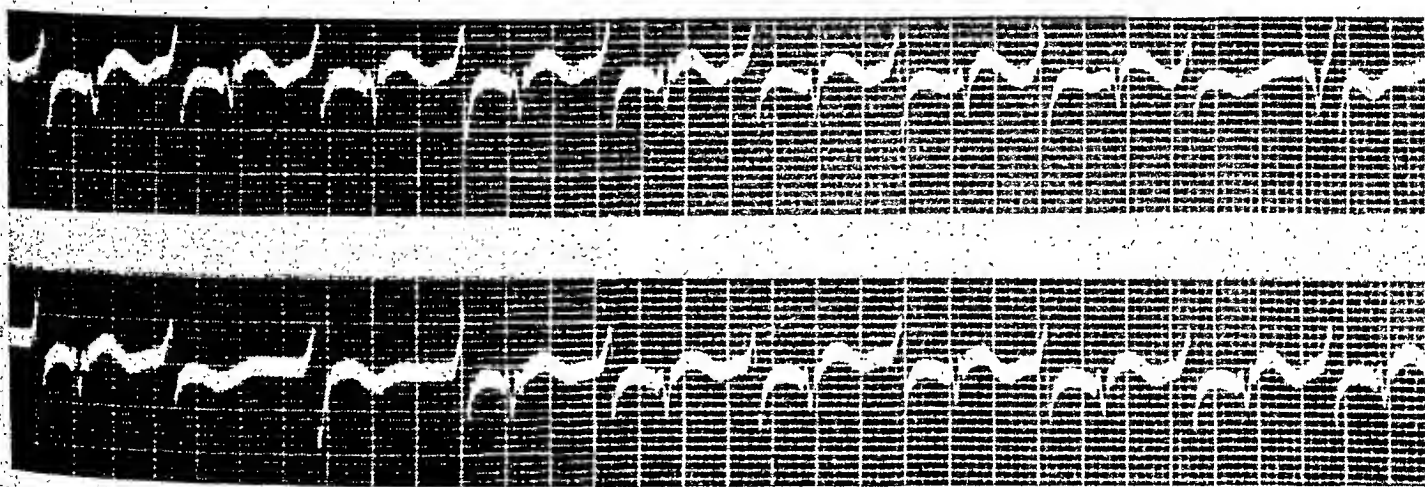


Fig. 35.—Incomplete A-V block (second degree). Continuous tracings from the mid-auricular level. Notice the auricular T wave when the A-V conduction fails.

Incomplete A-V Block: Fig. 35, a tracing made from a medium auricular level, shows this condition. The P wave is diphasic (PRs) and its voltage is greater than that of the ventricular complex. Sometimes auriculoventricular conduction fails and the auricular T wave is clearly discernible. Similar cases may be of interest for the study of auricular repolarization.

SUMMARY

The intracavity potential of the dog's heart in different experimental conditions was studied with unipolar leads. This study led to the following conclusions:

1. After ligation of the anterior descending coronary artery, the left intraventricular pattern shows depression of the RS-T segment, similar to that obtained on the posterior aspect of the heart in sites opposite to the infarcted zone. When no displacement of the RS-T segment is found, this is probably due to an incorrect placing of the electrode inside the cavity.

2. Consecutive to the ligation of the left circumflex artery the intracavity potential shows, in most of the cases, positive displacement of the RS-T segment, coincident with depression of this segment in tracings made from the epicardial surface of the injured zone. In a very few cases intracavity leads show no change while epicardial leads show a positive displacement of the RS-T segment.

3. Left and right intraventricular potentials were studied in experimental ventricular extrasystoles. When extrasystoles are initiated on the right side, the left intraventricular potential shows a diphasic QRS complex, with initial positivity of RS type; in the right intraventricular tracing, the QRS complex is always negative (QS). When ventricular extrasystoles are produced in the left ventricle, complexes of the RS type are obtained in right intraventricular leads, and complexes of QS type in leads from the left cavity. There is a very strikingly similar appearance in the pattern of intracavity potential of right ventricular extrasystoles and left bundle branch block, on the one hand, and right bundle branch block and left extrasystoles on the other.

4. After the right branch of the bundle of His was severed, intracavity potential patterns show the changes described by Wilson and associates: QS type complexes in left ventricular leads and RS type complexes in the right leads from ventricular cavity.

5. The morphology of the intracavity patterns after cutting the left branch of the bundle of His is similar to that found by Wilson and associates: QS type complex in leads from the right ventricular cavity and RS complexes in the left intraventricular tracing.

6. Complete section of the bundle of His was performed. The tracings obtained show in this case complete A-V block and idioventricular rhythm. The pattern of the intraventricular potentials is different from that found in experimental block of a single branch bundle. Ventricular complexes are never of the RS type, for they always show a slight initial negative wave.

7. After isolated section of one of the branches of the bundle of His, the QRS complex of the tracing taken inside the auricular cavity, at the side opposite

to that in which the cut was made, is similar to that found in tracings made from the homologous ventricular cavity. The tracing taken inside the auricular cavity on the same side as the block, however, does not show a ventricular complex of RS type but of qRs type.

The right intracavity potential of the human heart, in normal and pathologic conditions, was studied with unipolar leads. This study yielded the following results:

1. The normal tracing. When the electrode is located in the superior vena cava or near the sinus node, the P wave is negative (Pqs). This wave is diphasic (PRs) when the electrode is placed in the middle of the auricle. With the electrode in the lower portion of the same cavity, the diphasic P wave is predominantly positive (PRs); with the electrode in the ventricular cavity, the P wave is positive and of low voltage. The ventricular complexes taken inside the auricular cavity may have different morphology: QR, QRS, rSR' and RS. We label as "early" R the first positive deflection of the two latter types and relate it to septal activity. We designate as "late" R the positive deflection of the first two types, and the R' of the third, and relate it to the late activity of some muscular portions of the right ventricle. In tracings made from the ventricular cavity, the most frequent shape of the complex is RS. The early R is dependent upon septal activity and the S upon the activity of the free walls of both ventricles. In intracavity leads from both chambers the T wave is negative.

2. In right ventricular hypertrophy, the P wave is not modified. The ventricular complexes are of QR or qRs types. The "late" R increases in voltage and it is for this reason that we relate it to the late activity of some hypertrophied muscular portions of the right ventricle. Inside the ventricular cavity the tracing is similar to the normal one, the T wave being negative in both cavities.

3. In left ventricular hypertrophy, the P wave is not modified. The ventricular complex is similar at all auricular levels and is QS or QRS in type. The late R is absent or diminished. This is probably due to the strong vectorial forces that represent the activity of the hypertrophied free wall of the left ventricle. The ventricular tracing is always of the RS type. T is positive in both cavities.

4. In right bundle branch block the "late" R in tracings made at high auricular levels is very wide and bizarre and very similar to that seen in Lead VR in the same type of block. The tracing is of the QR type. In tracings made at lower auricular levels the complex is qRs in type with negative T wave, much like the tracing found in the animal after cutting the branch. In the intraventricular tracing the complexes are of RS type with a negative T wave. The general form is very similar to that found in the dog.

5. In left bundle branch block the ventricular complexes obtained from inside the auricle have only negative deflections (QS) with positive T waves. In intraventricular tracings the complex of great amplitude is QS with a positive T wave. The similarity to animal tracings is striking.

6. Right ventricular premature beats have the same characteristics as those experimentally produced in animals.

7. Intracavity potential changes in certain miscellaneous conditions were studied. These conditions included subendocardial ischemia, auricular flutter, and partial A-V block.

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Clinical Reports

THROMBOANGIITIS OBLITERANS IN THE NEGRO: REPORT OF A CASE AND REVIEW OF THE LITERATURE

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THE following case is presented as a proven instance of thromboangiitis obliterans in a Negro, an occurrence which is considered to be relatively rare.

CASE REPORT

J. E. C., a 30-year-old Negro man, was admitted to University Hospital in December, 1944, with a chief complaint of "infected toe." The immediate illness began four weeks before entry when the left great toe became "sore." A chiropodist trimmed the toenail and advised hot soaks. A week later the entire toe was fluctuant. "Numbness" became marked over the dorsal aspect of the left foot, and abnormal sweating was noticed in this area.

During the next two weeks various physicians were consulted. Many types of local treatment were attempted but the soreness progressed to a steady, severe, dull pain, present even at rest, and most severe in the calf and great toe of the left leg.

One week before admission the patient noticed that his left leg felt "cold" from toes to knee. In addition, the toes of the left leg had begun to turn "black" and appeared "withered." This, the fear of spreading infection, and the continued pain led him to seek hospital admission.

He denied pedal edema, tender subcutaneous nodules, intermittent claudication, or trauma to the legs during the four weeks prior to entry. Seven years before the present illness, however, when his job as a steel mill hooker required long hours of standing on a hot metal grill, the patient first noticed severe bilateral "arch pains" aggravated by walking, especially in cold weather, but relieved by resting during the walk. These pains recurred intermittently with exercise through five otherwise asymptomatic years. Two years before admission the patient's right great toe became "swollen and painful." Repeated visits to the outpatient department necessitated exposure to severely cold weather. Following one prolonged exposure the affected toe became "boggy" and amputation was advised and performed. No definite diagnosis was made at that time.

The past medical history was noncontributory except for the findings already mentioned. No history of syphilis was obtained. The patient had been a heavy smoker of cigarettes. The social history, obtained from the entire family, gave no evidence of intermarriage with the white race.

Physical examination showed a well-developed Negro of intelligent manner. The temperature, pulse rate, and respiratory rate were normal. The blood pressure was 140/106 in the right arm and 138/90 in the left arm. No blood pressure readings could be obtained in the legs.

Examination of the left leg revealed coldness to touch from patella to toes. An area of dry gangrene of waxy purple hue involved all toes and spread in a tapering band to the lateral dorsum of the foot, where the margin of the gangrenous area was sharply demarcated, and leathery black in color (Fig. 1). The dorsalis pedis, posterior tibial, and popliteal arterial pulsations could not be felt. The femoral arterial pulsation was palpable.

Examination of the right leg revealed skin which was scaly, but of normal temperature to palpation. The great toe had been amputated. The femoral pulse was palpable, but the dorsalis pedis, posterior tibial, and popliteal pulsations could not be felt.

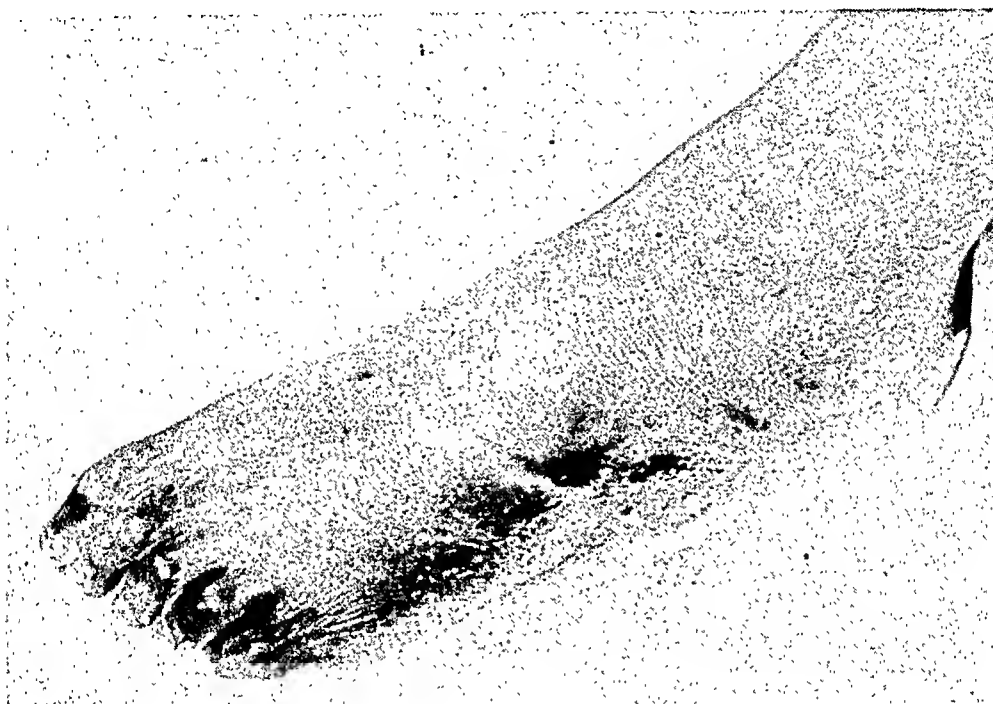


Fig. 1.—Area of dry gangrene with well-demarcated margin. Despite conservative therapy the area of involvement spread centrally necessitating major, though not radical, amputation. (Photograph from Dept. of Photography, Ohio State University.)

The radial, ulnar, brachial, and temporal arterial pulsations were not diminished, nor was there clinical evidence of abnormal arterial thickening.

Elevation of the feet produced minimal blanching of the plantar skin surfaces; upon dangling the feet return of apparently normal skin color was slightly prolonged.

All other physical findings were normal.

Laboratory Studies.—Quantitative dermathermic and qualitative oscillometric findings are shown in Table I. Blood studies, including a Kahn test and tests for sicklemia and for cold hemolysis were normal or negative. The glucose tolerance curve, blood uric acid, total protein and albumin-globulin ratio, cholesterol, and prothrombin level were also normal. Urinalysis, x-ray films of the chest and extremities, and examination of the cerebrospinal fluid were all negative.

Differential Diagnosis.—The history and physical examination placed the correct diagnosis in the field of peripheral vascular diseases. The patient's prolonged course, decreased arterial pulsations, and lack of systemic manifestations were sufficient grounds to rule out arterial embolism, Raynaud's disease, primary erythromelalgia, closure of an arterial aneurysm, and specific infections

TABLE I.

AREA EXAMINED	FINDINGS AFTER ONE HOUR IN CONSTANT (23° C.) ROOM TEMPERATURE	FOLLOWING SPINAL ANESTHESIA, WITHOUT USE OF VASOPRESSOR
Right knee	31.7° C. skin temperature	32.5° C. (+0.8°)
Right ankle	31.0° C. skin temperature	31.2° C. (+0.2°)
Dorsum right foot	32.0° C. skin temperature	31.6° C. (-0.6°)
Left knee	30.6° C. skin temperature	31.5° C. (+0.5°)
Left ankle	31.7° C. skin temperature	31.0° C. (-0.7°)
Dorsum left foot	30.9° C. skin temperature	30.8° C. (-0.1°)
Right popliteal space	Pulsations, low normal	No change
Right ankle	Pulsations, low normal	No change
Left popliteal space	No pulsations	No change
Left ankle	No pulsations	No change

known to cause vascular occlusions. The clinical differentiation of the more likely etiologies was very interesting.

Arteriosclerosis at the age of 30 years, limited to the legs, seemed unlikely, though "presenile arteriosclerosis" could be considered a diagnosis, or at least a terminological refuge. There was no history supporting a diagnosis of diabetic arteriosclerosis. Cold hemagglutination¹ was a possibility, since both acute episodes had started during a severe winter. In view of the patient's former occupation, the broad clinical entity termed pneumatic hammer disease² was considered. Sick cell anemia, syphilitic endarteritis, and periarteritis nodosa could not be eliminated as possibilities.

The diagnosis of thromboangiitis obliterans presented an impasse. The patient's age, the recurrent episodes of vascular occlusion, the rest pain, physical findings, and tendency towards spontaneous healing made thromboangiitis obliterans the most likely diagnosis. Only the racial axiom, still held by some, that this disease does not occur in full-blooded Negroes stood against the diagnosis.

Quantitative dermathermic and qualitative oscillometric findings were considered significant (Table I). The lack of response to spinal anesthesia was interpreted as indicating that the essential pathology was occlusive, not vasospastic, in nature.

By exclusion, the diagnosis lay between gangrene due to arteriosclerosis and gangrene due to thromboangiitis obliterans. The therapeutic implications of these two conditions are usually quite different, and the difference is of importance to a patient in the wage-earning years of life.

Both conditions deserve, and may respond to, a well-rounded course of conservative therapy. Even so, the former will more often require amputation, and at a level well above the gangrenous tissue. Thromboangiitis obliterans, however, has a somewhat more hopeful prognosis, and should amputation be necessary it is seldom justifiable to select a high amputation site.

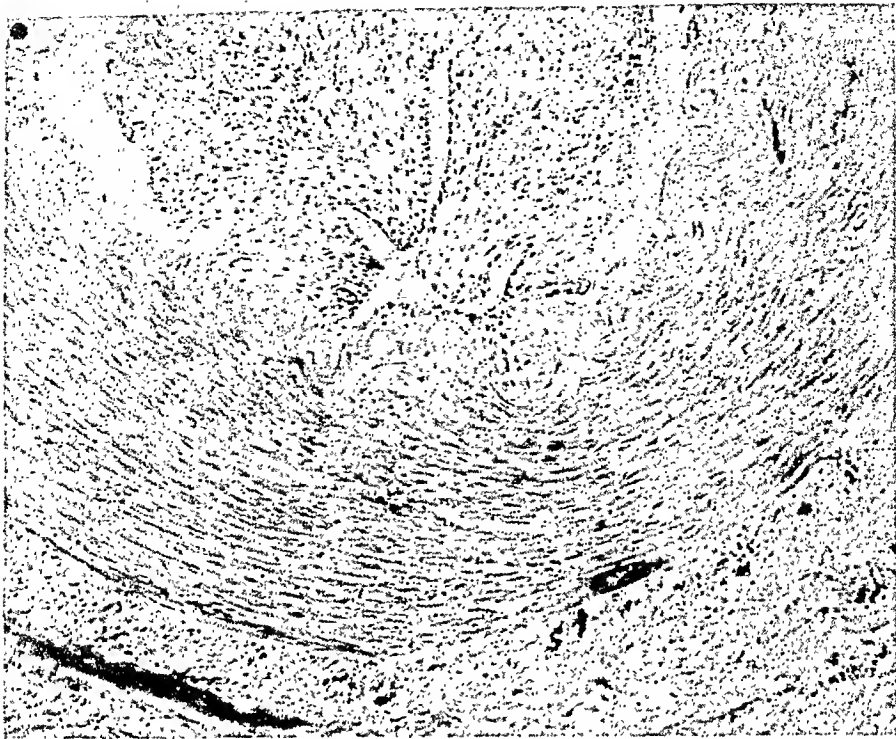


Fig. 2.—Section through the posterior tibial artery, showing a well-organized and canalized arterial thrombus occluding the vessel lumen. H. and E. stain, reduced from magnification of $\times 175$. (Photograph from Army Medical Museum, Washington, D. C.)



Fig. 3.—Section through the posterior tibial artery, showing the internal elastic lamina, seen as a wavy black line, intact. The media and adventitia are normal, and the arterial thrombus is again demonstrated. Weigert's elastic tissue stain, reduced from a magnification of $\times 675$. (Photograph from Army Medical Museum, Washington, D. C.)

Clinical Course.—On conservative therapy, including cessation of smoking, there was no improvement. The area of dry gangrene spread centrally and the severe rest pain was relieved only by continued sedation. Therefore, on the nineteenth hospital day, an amputation* was performed through the lower third of the left tibia. It was noted during the operation that the severed blood vessels showed oozing, without brisk bleeding. The course of postoperative healing was excellent.

Pathologic Findings.†—Dissection of the amputation specimen revealed, in addition to the gangrene described, some thickening and rigidity of all major arteries. This, however, was not marked; the veins appeared normal, and no matting of artery, vein, and nerve was seen.

Sections of all major vessels were taken at various levels. Microscopic sections were stained with hematoxylin and eosin, and with Weigert's elastic tissue stain.

The major finding was a marked degree of arterial thrombosis (Fig. 2). Elastic tissue staining revealed that the intima was normal, with the internal elastic lamina intact (Fig. 3). The arterial thrombi showed advanced organization and canalization.



Fig. 4.—A focal collection of inflammatory cells is seen in the periadventitial connective tissue between artery below (left) and vein above. H. and E. stain, reduced from magnification of x175. (Photograph from Army Medical Museum, Washington, D. C.)

The veins did not show thromboses. There was, however, a moderate thickening of their walls. Focal infiltrations of inflammatory cells were present in the periadventitial tissues (Fig. 4). Binding of artery, vein, and nerve by fibrous tissue proliferation was not observed.

*Amputation was performed by Dr. Donald W. Traphagan of the Department of Surgery.

†Dr. Charles Chesner and Dr. H. B. Davidson of the Department of Pathology reviewed these findings and independently made a diagnosis of thromboangiitis obliterans.

DISCUSSION

Thromboangiitis obliterans is rarely seen in Negroes. Gemmil's original case³ was accompanied by an abbreviated report of the pathologic findings. A single case report⁴ by Parson did not include the pathologic findings. Smith also reported a case⁵ with an excellent history and conclusive physical findings, but lacking pathologic confirmation. Yater has presented a thorough study of five cases⁶ which included precise pathologic findings. Although every case showed clinical or serologic evidence of syphilis, one is impressed by the fact that the findings are those of thromboangiitis obliterans in all but the academic sense that in each case the disease may have been on the basis of syphilitic endarteritis. He points out, and we believe justifiably so, that there are grounds for doubt as to any connection between syphilis and peripheral vascular disease,⁷ despite the early studies of Warthin.⁸

Yater⁹ has recently described a previously unrecognized form of widespread arterial occlusion, seen in Negroes, and marked by medial fibrosis. Our case does not resemble this entity, but it is of interest to note his discussion mentioning a case of thromboangiitis obliterans in the Negro recently observed on his service.

Warshawsky,¹⁰ alone, has reported a case fulfilling the criteria of "racial purity, absence of luetic involvement, and adequate pathological evidence." We feel that it is of more than academic importance to review briefly: (1) exactly what constitutes "adequate pathological evidence" and (2) whether we are not restricting our viewpoint to the detriment of patients who will not fit a narrow category.

When Buerger¹¹ first described the three distinct phases in the pathology of thromboangiitis obliterans, he pointed out that clinical symptoms referable to vascular occlusion actually reflect the end stage in the pathologic sequence. The earlier phases, leucocytic infiltration of the veins and the formation of miliary giant cell foci, do have a clinical counterpart, namely, migrating phlebitis. When treatment is considered, however, these findings are of little moment compared to the recanalization and slow vascular occlusion seen in the final pathologic stage, repair.

The implications beyond these findings are the basis for the often stressed^{12,13,14} clinical concept: "There are few procedures more unjustifiable than radical amputation of a limb which might have sought its own level of disability."

In view of this, we do not feel that there is sufficient reason to restrict the diagnosis of thromboangiitis obliterans to those cases showing the early as well as the late phases of the pathologic sequence.

SUMMARY

A case of thromboangiitis obliterans occurring in a Negro is described. A review of all previous reports of this uncommon combination is presented. Viewpoints on what constitutes adequate pathologic evidence of this condition are considered, and treatment is discussed in relation to the sequence of pathologic changes.

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PERFORATION OF THE INTERVENTRICULAR SEPTUM IN A CASE OF SUBACUTE BACTERIAL ENDOCARDITIS

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PERFORATION of the interventricular septum due to subacute bacterial endocarditis is a rare condition.^{1,2} Wilson³ reported three cases of mycotic aneurysm with perforation of the interventricular septum complicating subacute bacterial endocarditis. The purpose of this paper is to present a case of subacute bacterial endocarditis complicated by perforation of the interventricular septum diagnosed during life and confirmed at post-mortem examination.

CASE REPORT

D. P., a white man, 37 years of age, entered the hospital on April 9, 1945, with complaints of fever, night sweats, and dyspnea. The patient was well until three months prior to admission, when he began to experience chills, fever, dyspnea, and palpitation. He went to see his local doctor who advised him to remain in bed; however, no specific medications were ordered. His condition grew progressively worse; his daily fever continued, he noted the appearance of some reddish spots on the palmar aspects of his finger tips, and he lost about twenty pounds during the two months prior to admission. He complained of burning of the finger tips and pain beneath the left costal margin. There was no history of symptomatology referable to rheumatic fever at any time prior to the present illness. At about the age of 17 years, during a routine physical examination, he was told that he had heart trouble. The remainder of his history was noncontributory.

Physical examination on admission revealed the following positive points: The temperature was 101°F.; pulse, 130 per minute; and blood pressure, 140/95. Numerous carious teeth were present and the gums bled on slight pressure. Murmurs interpreted as being indicative of aortic stenosis, mitral stenosis, and insufficiency were present. The spleen was palpable 4 to 5 cm. below the left costal margin, and was tender.

Laboratory work on admission revealed 4.3 million red blood cells with 76 per cent hemoglobin, a white blood cell count of 12,000 with 86 per cent polymorphonuclears, 2 per cent eosinophiles, 1 per cent monocytes, and 11 per cent lymphocytes. Sedimentation rate was 60 mm. per hour. Urinalysis on admission revealed 20 to 30 white blood cells and 40 to 50 red blood cells per high power field. Fourteen blood cultures, including four arterial blood cultures, were negative. An x-ray film of the chest showed cardiac enlargement to the left. An electrocardiogram showed R₁, R₂, and R₄ slurred, sinus tachycardia, and T₁ and T₄ inverted. Repeated agglutinations for typhoid, paratyphoid, and *Brucella* were negative.

A diagnosis of subacute bacterial endocarditis was based on the past history, and presence of cardiac murmurs, continued fever, evidence of emboli, and splenomegaly. The patient continued to run fever, and despite the absence of a positive culture we did not feel justified in withholding treatment. Therefore, 200,000 units of penicillin per twenty-four hours were administered daily in divided intramuscular doses every two hours for four weeks, along with hepariniza-

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tion to maintain a clotting time between 30 and 60 minutes (Lee and White) during the initial two weeks of therapy. Sulfadiazine was also employed in dosage of 1 Gm. every four hours during the entire period of treatment. He became afebrile on the fifteenth day of therapy, his febrile episodes during therapy prior to this being accounted for on the basis of heparin reactions. The patient remained afebrile after completion of therapy, and his condition improved to the point where he could be discharged three weeks later.

He was followed in the outpatient clinic, with blood cultures remaining negative. After returning home the patient remained afebrile; however, he noted a gradually increasing weakness, and fainted on exertion three times. He also complained of dyspnea on exertion, and his feet would swell in the afternoon. Since his discharge he had noted no costovertebral angle pain, petechiae, or gross hematuria. Because of his gradually increasing weakness, he was readmitted to the hospital on Nov. 1, 1945. Physical examination on his second admission revealed temperature of 98.6° F., pulse 88, blood pressure 145/69. In addition to the cardiac findings on the previous admission the following new signs were found: A systolic thrill was felt best at the left fourth intercostal space near the sternum, and a rough, loud, long, low-pitched systolic murmur was heard best over the fourth left intercostal space near the sternum, and over the lower end of the sternum. The other murmurs heard on the previous admission were still audible and unchanged from the time of discharge. The spleen had increased in size. Laboratory work showed 10 Gm. of hemoglobin and a white blood cell count of 3,900 with 65 per cent polymorphonuclear cells and 35 per cent lymphocytes. Repeated urinalyses revealed 20 to 60 red blood cells per high power field, hyaline casts, 3-plus albumin, and specific gravity varying from 1.017 to 1.014. Urea nitrogen varied from 21 to 40 mg. per cent. Repeated Fishberg concentration tests showed specific gravity varying from 1.013 to 1.016. Phenolsulfonphthalein excretion varied from 35 to 45 per cent. Nine negative blood cultures were obtained. He displayed signs of renal damage and cardiac insufficiency in the presence of negative blood cultures, and an afebrile state which we decided represented the bacteria-free stage of subacute bacterial endocarditis. The other speculation made at this time concerned the etiology of the murmur first noted on his second admission. We believed that there was an extension of the vegetation from the aortic valve on to the interventricular septum with a subsequent perforation of the septum producing a communication between the right and left ventricles, resulting in the appearance of the murmur described above. During the next few months the patient's condition grew progressively worse with renal and cardiac failure becoming prominent. About two weeks prior to the patient's death the murmur believed to be due to an interventricular septal defect disappeared.

Necropsy Report.—Permission was granted for a partial autopsy.* The heart weighed 589 grams. The valvular measurements were as follows: tricuspid, 12.0 cm.; mitral, 11 cm.; pulmonary, 8.0 cm.; and aortic, 10 centimeters. The wall of the left ventricle was 1.7 cm. in thickness, and that of the right ventricle, 0.4 centimeters. There was a small amount of subepicardial fat. On the anterior surface of the left ventricle, just lateral to the interventricular groove, there was seen a fibrous adhesion measuring 0.5 cm. in length. Both ventricles were dilated. The myocardium was dark red and flabby. The papillary muscles were a mottled yellow-red. The chordae tendineae of the mitral valve were thickened and shortened. The posterior valve leaflet was thickened and partially calcified, with many small nodules seen on its surface. MacCallum's area was roughened. All cusps of the aortic valve had rolled edges, with 0.1 cm. calcified nodules being most prominent along the line of closure and being disseminated throughout the aortic and ventricular surfaces of the cusps. There was an 0.8 cm. nodular elevation on the right posterior cusp. There was widening of all commissures, but the attachment was at the normal level. At the base of the right posterior cusp was an oval perforation measuring 0.4 cm. by 0.5 cm., which connected the left and right ventricles. This perforation traversed the membranous portion of the interventricular septum. The edges were smooth, round, grey, firm, and fibrous. This perforation was covered on its left ventricular aspect by a fibrinous sheath. Just to the left of this perforation, at the base of the left posterior cusp, was an additional 0.2 cm. pocket which extended into, but did not perforate, the interventricular septum (Fig. 1). The tricuspid

*Autopsy was performed by Dr. Philip Pizzolato.



Fig. 1.—Left ventricular aspect of perforation in interventricular septum.



Fig. 2. — Right ventricular aspect of perforation in interventricular septum.

valve showed a slight thickening of the cusp edges. On the right side the perforation was seen at the base of the medial leaflet of the tricuspid valve (Fig. 2). The pulmonic valve was normal except for a few firm nodules, 0.1 cm., on the ventricular surfaces of all cusps. The coronary arteries were patent throughout. A few yellow atheromatous plaques were seen in the aorta.

Microscopic sections of the mitral valves stained with hematoxylin and eosin revealed a large amount of fibrosis, some of which was completely hyalinized, and areas of chronic granulation tissue characterized by dilated, thin-walled capillaries surrounded by lymphocytes, macrophages and a few plasma cells. In these areas of fibrosis there were small irregular deposits of calcification. Extravasated red blood cells were seen in another area adjacent to the chronic granulation tissue, and numerous macrophages filled with hemosiderin pigment were present. Gram stain of the mitral valve showed no bacteria present. The aortic valve revealed a large amount of hyalinized connective tissue in which only a few pyknotic elongated nuclei were encountered. In less hyalinized places there were areas of chronic granulation tissue with fibrosis similar to those of the mitral valve. Areas of calcification, as previously described, were seen. Gram stain of the aortic valve showed no bacteria present.

Microscopic sections of the myocardium revealed myocardial fibers of the usual size. The cross striations were not prominent. Adjacent to some of the blood vessels in the connective tissue were lymphocytes and macrophages; however, no true Aschoff cells were seen. Microscopic section through the area of perforation showed a large amount of fibrosis; at the periphery chronic granulation tissue was composed of partially hyalinized capillaries surrounded by macrophages, lymphocytes, and a few plasma cells. Examination of the kidneys revealed numerous petechiae in the cortex. The line of demarcation between medulla and cortex was distinct. The cortical and medullary striations were prominent. Microscopic examination of the liver, spleen, and kidneys revealed marked congestion. The lungs showed bronchopneumonia and marked congestion.

SUMMARY AND CONCLUSIONS

A case of subacute bacterial endocarditis has been presented in which treatment with penicillin caused the establishment of a bacteria-free stage. A perforation of the interventricular septum was diagnosed during life and confirmed at post-mortem examination. This case demonstrates the need for an early diagnosis and institution of treatment with penicillin, in adequate amounts over a sufficiently long interval of time, if one is to avoid permanent renal and cardiac damage which will cause the patient's death despite the disappearance of the vegetations from the heart valves.

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DISSECTING ANEURYSM WITH HEMOPERICARDIUM

REPORT OF A CASE

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PHYSICIANS are rapidly becoming more aware of the possibility of dissecting aneurysm in cases of sudden thoracic pain. Shennan,¹ in his comprehensive review of the literature up to 1933, accepted six cases in which a correct diagnosis had been made ante mortem. Since then, however, many cases have been diagnosed, and there have been excellent recent reviews of the subject.²

The most frequent complication of dissecting aneurysm, terminal rupture into the pericardial sac, has occurred in approximately 70 per cent of the previously reported cases. Only one other case³ was encountered in which preterminal tamponade occurred; this was immediately recognized and temporarily relieved by pericardicentesis. In the following case it seems evident that the tamponade occurred concurrently with the original dissection, as signs of cardiac compression, notably a marked pulsus paradoxus, were noted shortly after the onset of pain and persisted until death two days later. The presence of these signs greatly aided in the establishment of a clinical diagnosis.

CASE REPORT

D. R., a 67-year-old businessman, was brought to the emergency room of the Toledo Hospital at 11:10 P.M., Dec. 24, 1945. The complaint was that forty-five minutes before, while pushing his automobile, he had suddenly developed a severe retrosternal pain which was constant and did not radiate. Cursory examination revealed findings not incompatible with coronary thrombosis, and electrocardiographic confirmation of this tentative diagnosis was immediately sought.

The electrocardiogram (Fig. 1) showed sinus rhythm with marked left axis deviation. There was no displacement of the RS-T segment nor other QRS or T-wave changes that could be interpreted as even suggestive of myocardial ischemia or recent infarction.

From his wife it was learned that he had had hypertension for a number of years. His blood pressure had been 156/110-100 in 1940, and 168/104 in 1941, as recorded on two previous admissions for unrelated complaints. The blood Wassermann and Kline had been negative in 1940. Otherwise the past history was essentially negative.

The physical examination revealed a well-developed and well-nourished elderly white man of hypersthenic habitus, acutely and severely ill. He was sweating profusely. Neither dyspnea nor cyanosis was evident. He was partially confused and disoriented so that it was not possible to obtain a detailed description of the nature of his pain. Temperature was 98°F. Head, eyes, ears, nose, and throat were negative. The neck was flaccid, and the jugular veins were not con-

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spicuous. There were fine inspiratory râles in both lung bases. Respirations were 16 per minute and neither predominately thoracic nor diaphragmatic in type. The pulse rate was 76 per minute, and the volume seemed equal in both radial arteries. Slight waxing and waning of the radial pulse related to respirations was noted. On sphygmomanometry the beats faded out on inspiration, so that the systolic pressure during that phase was approximately 30 mm. lower than

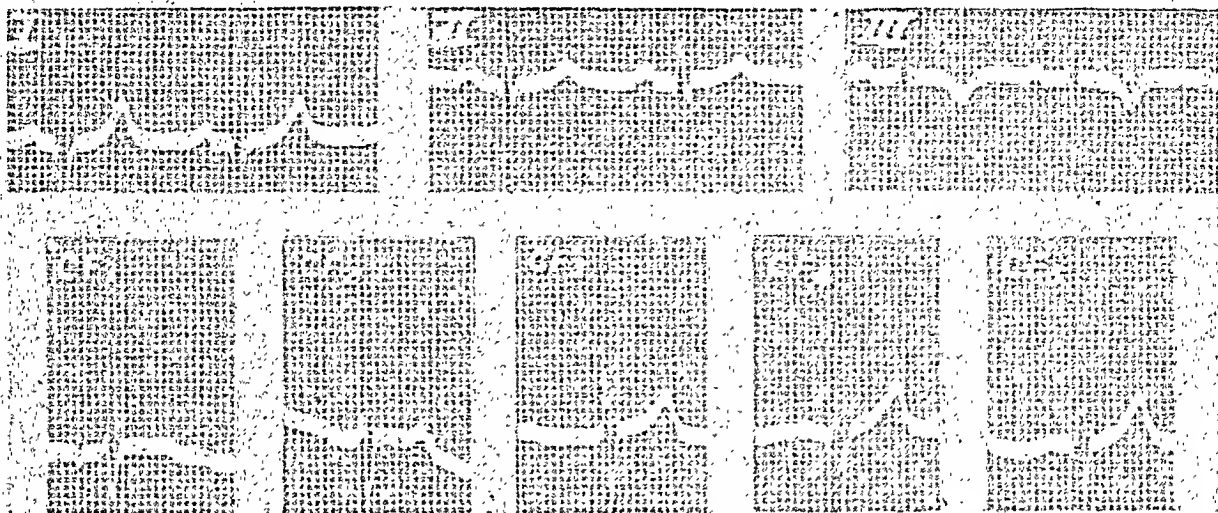


Fig. 1.—Electrocardiogram showing left axis deviation without other abnormality.

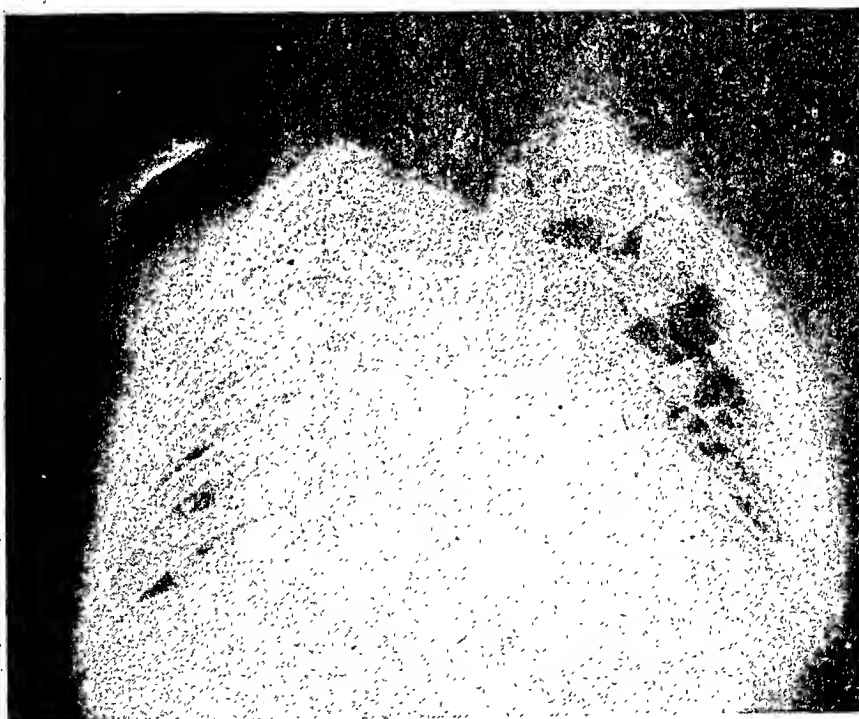


Fig. 2.—Dissecting aneurysm. Two-meter overhead film taken post mortem. There is a generalized enlargement of the cardiac shadow. The diaphragms are at a high level. The lung markings are not significant.

during expiration. The blood pressure was 165-135/95. The apical impulse was in the sixth intercostal space 5 cm. to the left of the midclavicular line. No thrills were present. The rhythm was regular. There was a blowing, grade 3, systolic murmur which was audible over the entire precordium, but most marked in the aortic area. The second sound at the base was not accentuated, and there was no diastolic murmur.

The liver edge was barely palpable beneath the costal margin, and the upper border of hepatic dullness was in the fifth intercostal space. Otherwise, the abdomen was negative. There was no edema of the extremities and no changes or inequalities in the reflexes.

A diagnosis of dissecting aneurysm of the aorta with hemopericardium was ventured at this time.

Laboratory studies showed a hemoglobin of 15.1 grams, 5,510,000 red cells, leucocytosis of 20,200 with 66 segmented polymorphonuclear leucocytes, 23 band forms, 4 mature lymphocytes, 6 monocytes, and 1 eosinophile. The erythrocyte sedimentation rate was 18 mm. per hour. A trace of albumin and a moderate number of coarse granular casts were found in the urine specimen. The nonprotein nitrogen was 60 mg. per 100 c.c. of blood on December 26.

The morning after admission the status of the patient had not changed significantly. Morphine and dilaudid had been used to control pain. The paradoxical pulse was noted again in all palpable arteries. The blood pressure was 175-150/105 in the right arm; slightly lower in the left.

The second morning after admission the temperature had risen to 102.8°F. A chest film made with a portable apparatus showed marked mediastinal widening and cardiac enlargement, but was deemed unsatisfactory for interpretation. A second electrocardiogram was similar to the first. On the evening of the second day the patient showed periorbital edema, distended jugular veins, and cyanosis. The blood pressure was 180-150/120. Cardiac and pulmonary findings were the same as on admission. Venous pressures were obtained by direct manometric method in both arms and the left leg; these were equal at 200 millimeters. A 22 gauge needle was used, and respiratory variations in venous pressure were not observed. Circulation times were attempted, but the patient was unable to give an accurate end point. It was decided to transport the patient, in bed, to the x-ray department for a more satisfactory film. In transit he had a second severe chest pain, became intensely cyanotic, and died within a few minutes, forty-five hours after his first attack. A two-meter overhead film was taken postmortem (Fig. 2).

*Autopsy.**—The positive findings were limited to the heart, aorta, and kidneys. The heart and pericardium extended to the seventh interspace on the left side and to the anterior axillary line. The right side extended slightly to the right of the right sternal line. There was considerable effusion of blood in the soft tissues of the mediastinum. The pericardial cavity contained approximately two pints of blood, largely in blood clots. The blood had apparently escaped through a tear in the adventitia of the aorta and another tear in the intima.

The heart weighed 500 grams. There was enlargement of the left ventricle. The pericardium was covered by a moderate amount of subepicardial fat which was distributed in normal depots. The left coronary artery was thickened and showed partial occlusion of the lumen due to intimal proliferation. The left ventricular wall measured 2 cm. at the base and 1.2 cm. at the apex. The right ventricular wall measured 4 mm. The left ventricular and auricular chambers were dilated. The valve leaflets showed no gross abnormalities. The circumferences of the valves were within normal limits. The mouths of the coronaries were patent. The endocardium was smooth and glistening.

The aorta was of decreased elasticity and of average width. The intima showed areas of thickening, but there was no necrosis or calcification. There was a tear of the intima halfway across the aorta, 5.6 cm. above the aortic leaflets. There was separation of the aorta extending to the renal arteries and presence of large amounts of fluid and clotted blood in the tissues. The separation was between the intima and part of the media, and between the media and adventitia. There was a tear in the adventitia with blood in the soft tissues. Sections of the aorta showed hemorrhages and patchy areas of Erdheim's medial necrosis.

The kidneys weighed 350 grams. The capsules stripped with some difficulty leaving an evenly granular surface. The cut surface showed a narrow cortex with indistinct striations. The glomeruli were gray pin points. The medulla was purple. The pelves and ureters were normal.

Cause of death: Dissecting aneurysm of aorta and hemopericardium.

*Performed by Dr. Bernhard Steinberg.



Fig. 3.—Heart and aorta. The intima with a part of the media is separated from the remaining coats, part of the media, and adventitia by fresh and clotted blood.

COMMENT

The mode of production of the signs of cardiac compression in pericardial effusion has been investigated⁴ and found to be dependent upon increase in intrapericardial pressure. In inflammation of the pericardium the normally inelastic membrane becomes dilatable, as was early commented upon by Barnard⁵ and Mackenzie.⁶ In noninflammatory pericarditis, however, a small amount of fluid suffices to increase greatly the intrapericardial tension with the production of



Fig. 4.—Dissecting aneurysm. Aorta $\times 100$. The diffuse black area represents blood in the media. The smaller black dots are areas of medial necrosis of Erdheim.



Fig. 5.—Dissecting aneurysm. Aorta. Cystic area in the wall of aorta with honeycombing effect. The cyst is lined by tall columnar epithelium.

the paradoxical pulse and other signs of cardiac embarrassment. When the height of the intrapericardial pressure equals the venous pressure, the circulation is brought to a standstill, as shown by Kuno.^{4,h} From these considerations it is apparent that a sudden tamponade, as in hemopericardium from dissecting aneurysm or stab wounds,⁷ would be expected to produce a greater increase in the intrapericardial pressure than the gradual accumulation of a much larger amount of fluid in pericarditis.

In the case presented here the pulsus paradoxus, or Griesinger-Kussmaul sign,⁸ first focused attention upon the pericardium. The possibility that the respiratory variation in systolic pressure may have been produced by partial occlusion of the aortic lumen by intramural extravasation of blood without hemopericardium is quite unlikely and is not in accord with the experimental observations of Katz and Gauchat.^{4,c,d}

These workers arrived at the following conclusions in their study of pulsus paradoxus: "With the pericardium distended with fluid, not only is the flow of blood into the heart impeded, but the inflow also varies during inspiration and expiration, owing to the fact that the respiratory variations of intrathoracic pressure do not affect the intrapericardial and intracardiac pressures as much as those on the entering veins. This causes a smaller difference of pressure between the veins and heart during inspiration and allows less filling of each ventricle. Consequently, a paradoxical pulse probably appears in both pulmonary and systemic circuits, but obviously the arterial pulsus paradoxus is due to the impaired inflow into the left ventricle."

SUMMARY

A case of dissecting aneurysm with hemopericardium is presented. This diagnosis was made two days before death on the basis of the history, negative electrocardiographic findings, and signs of cardiac compression, especially the pulsus paradoxus. The physiologic basis of these signs is reviewed, and the likelihood of their occurrence in hemopericardium is suggested.

Appreciation is due Dr. Steinberg, Dr. N. Worth Brown for his valuable suggestions and criticism, and Dr. Frank Clifford for his permission to report this case.

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SPONTANEOUS MEDIASTINAL EMPHYSEMA WITH ACUTE RIGHT VENTRICULAR STRAIN

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SPONTANEOUS mediastinal emphysema is uncommon and still unfamiliar to many clinicians; nevertheless, reports of this condition appear in the literature more and more frequently. The occurrence of interstitial emphysema of the lungs and of mediastinal emphysema has been recognized for years. It is not rare following stab wounds or other trauma of the chest, as the result of the stresses of various respiratory diseases in childhood, and also following the use of positive pressure intratracheal anesthesia.

A case of pneumomediastinum has been observed which demonstrates what has been found experimentally but observed in no previous case: namely, the development of acute cor pulmonale during an attack of mediastinal emphysema without discernible pneumothorax.

CASE REPORT

A 16-year-old Negro boy was admitted to the hospital complaining of soreness in the neck and chest. Two days before admission, headache and malaise appeared. The day before admission he awoke with dyspnea and slight nonproductive cough. That evening he first developed pain and soreness of the chest and neck, which was aggravated by coughing and swallowing. This pain was localized over the precordium and anterior portion of the neck. There was moderate malaise but no nausea or vomiting. The patient had had uncomplicated measles and pertussis in early childhood. For several years he had suffered with bronchial asthma which improved with treatment. In the two years before admission, asthmatic attacks occurred only with upper respiratory infections.

On admission the temperature was 101.2°F., the pulse rate, 88; and respirations, 20 per minute. The blood pressure was 100/70. The patient, a well-developed, slender lad, complained of dyspnea and severe pain beneath the sternum and in the anterior neck. The pupils were equal and reacted to light and accommodation. Ophthalmoscopic examination was negative. The ears were normal. The nasal mucous membranes were congested and there was some mucoid discharge. The tonsils were enlarged and cryptic, with exudate in the crypts. The neck was held stiffly and the patient complained bitterly of pain in the anterior cervical region on flexion and extension. The cervical and submaxillary lymph nodes were slightly enlarged and firm. The chest was somewhat emphysematous and there was definite limitation of expansion of the left thorax. Percussion revealed resonance throughout, and tactile fremitus was normal. Breath

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sounds, however, were asthmatic, with many coarse râles and rhonchi. The area of cardiac dullness was of normal size; the heart sounds were normal and no murmurs were audible. The abdomen was negative. Tendon reflexes were sluggish and Kernig's sign was absent.

Laboratory Findings.—Urinalysis was essentially normal except for rare granular casts and 2 white blood cells per high power field. The blood examinations showed 16.0 Gm. of hemoglobin, 5,640,000 erythrocytes, and 10,400 white blood cells, of which 84 per cent were polymorphonuclears, 2 per cent eosinophiles, 12 per cent lymphocytes, and 2 per cent monocytes. The sedimentation rate was 6 mm. in one hour. The blood sugar was 99 mg. per cent. The non-protein nitrogen was 27 mg. per cent. The blood Wassermann was negative. The spinal fluid showed a normal pressure, three lymphocytes, a total protein of 15 mg. per cent, and a negative Wassermann.



Fig. 1.—Roentgenogram of chest demonstrating air in the mediastinum.

On the day after admission, loud crackling sounds were heard over the entire precordium; the accentuation was synchronous with the heart beat. This sound resembled most closely the crunching of cellophane, and was heard to the left as far as the heart sounds were audible. The area of cardiac dullness was completely obliterated at this time. There was no subcutaneous emphysema or emphysema of the neck tissues. Pain in the substernal area and in the neck became extremely severe. Examination of the lungs revealed only suppression of breath sounds over the left chest anteriorly. By the following day symptoms were relieved slightly, although the crunching precordial sounds were still present. Within the next few days the area of cardiac dullness became percussible and the bruit over the heart disappeared entirely. All symptoms gradually cleared.

For the first three days of hospitalization the patient's temperature ranged between 99 and 101.6°F.; thereafter it was normal. The white blood cells rose to 16,200, with 91 per cent polymorphonuclear cells, and then fell to 8,550. The blood pressure ranged constantly about 110/60. The circulation time at the height of the illness was 13 seconds (arm-to-tongue with decholin); venous pressure was 120 mm. of normal saline. The sputum was negative for tubercle bacilli and the tuberculin test was negative (1:1,000).

Roentgen Examinations of Chest (Figs. 1 and 2).—Films made on the *first* day showed the chest to be emphysematous and revealed fibrosis in both lungs. The findings suggested an asthmatic type of chest with no tuberculosis or pneumonia. The heart was normal. On the *second* day a fluoroscopic examination showed the left diaphragm to be depressed and limited in motion. Air was seen in the anterior and posterior mediastinum. No pneumothorax was observed. Films on the *second* day confirmed the presence of air along the left mediastinal border and adjacent to the pericardium, both anteriorly and posteriorly. The air extended much higher than the pericardial attachment. There was no visible pneumothorax. The lungs showed increased bronchovascular markings. On the *eighth* day films showed much less air along the left border of the pericardium and mediastinum. On the *fourteenth* day fluoroscopic examination showed that both diaphragms moved well and that the heart was normal and the lungs clear though emphysematous.



Fig. 2.—Left lateral roentgenogram also demonstrating pneumomediastinum.

Electrocardiograms (Fig. 3, A, B, and C).—Tracings made on the *third* day showed a deep S wave and a diphasic T wave in Lead I. In Lead II the P waves were peaked and the T waves of low amplitude. The findings in Lead III were peaked P waves, deep Q waves; and diphasic T waves of small amplitude. In Lead CR₄ the T waves were diphasic. These findings were interpreted to indicate right axis deviation and acute right ventricular strain. Tracings made

on the *fifth* day showed the P waves to be normal. There was a persistence of deep S waves in Lead I and Q waves in Lead III. The T waves were returning toward a normal appearance. Tracings taken on the *thirteenth* day showed the T waves to be entirely normal.

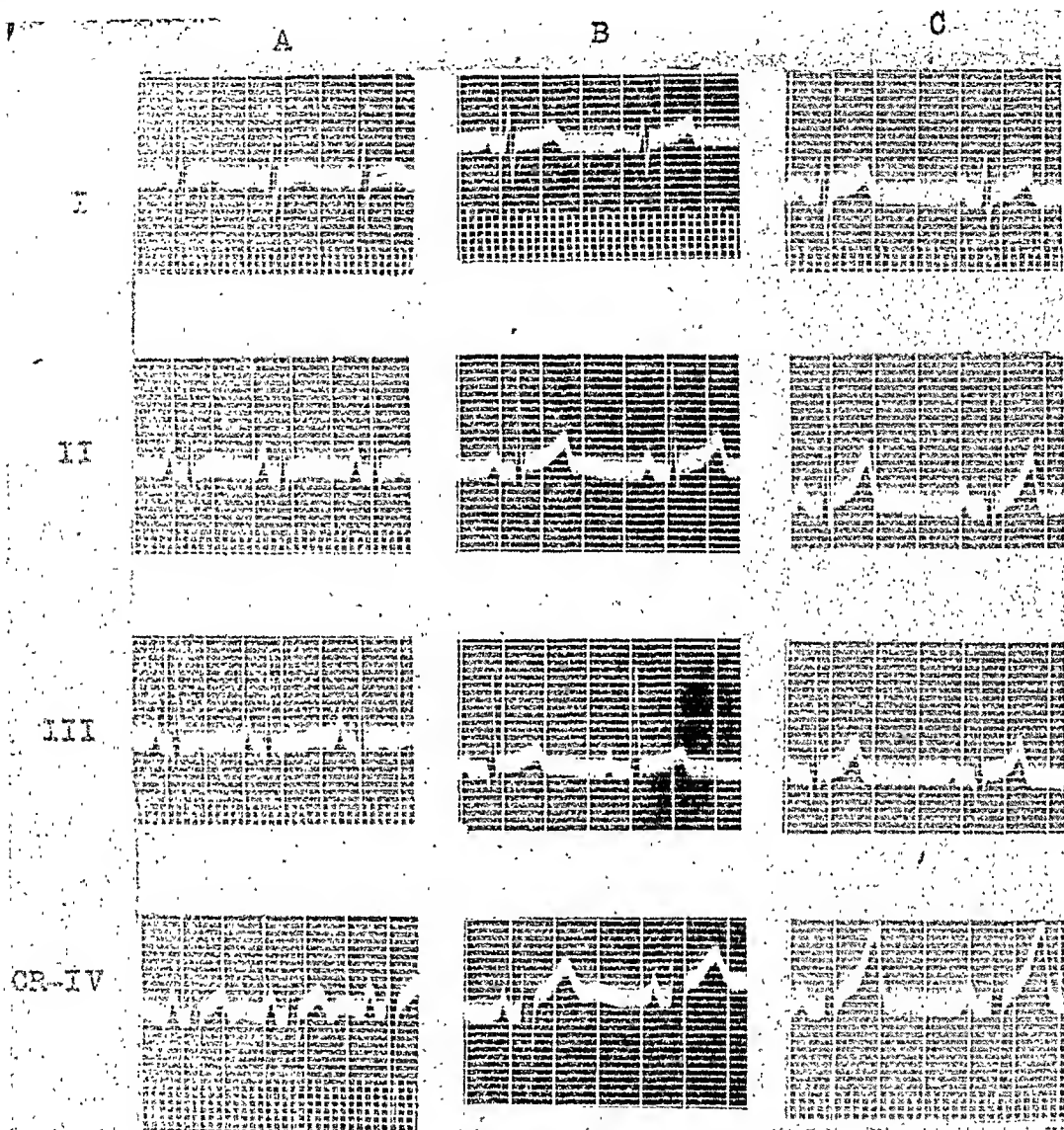


Fig. 3.—Electrocardiograms taken: A, third day; B, fifth day; and C, thirteenth day after admission.

DISCUSSION AND COMMENT

Increasing numbers of cases of spontaneous mediastinal emphysema, with or without complicating pneumothorax, are being reported in adults. Hamman¹ was the first to recognize the significance of this condition and to describe the clinical findings. In 1934, he presented two cases and has since added six others.²¹ Since its first description, further cases have been reported by Scott,² McGuire and Bean,³ Morey and Sosman,⁴ Wolff,⁵ Matthews,⁶ Pinckney,⁷ Caldwell,⁸ Styron,⁹ Griffin,¹⁰ I. Miller,¹¹ Murphy and Zeis,¹² Meek,¹³ Kellogg,¹⁴ Lintz,¹⁵ Adcock,¹⁶ Munroe and Webb,¹⁷ Greene,¹⁸ Palatucci and Knighton,¹⁹ and H. Miller.²⁰

In most of the reported cases, the clinical symptoms and signs have been similar, and have followed Hamman's original description¹ of the syndrome which has been restated in all subsequent discussions. The essential features are precordial and substernal pain of rapid or gradual onset in a basically healthy person or occasionally in one with a previous history of asthma. The appearance of the pain may be so dramatic as to simulate myocardial infarction, dissecting aneurysm, pericarditis, or mediastinitis; its distribution also may resemble these conditions. Contrary to Hamman's original statement that there are no constitutional symptoms or alterations of temperature, pulse, respiration, and leucocyte count^{21b}; a few authors have reported cases presenting aberrations of these features.^{3,15,20} In practically all the reported cases, the process was suspected because of a crunching sound heard over the precordium during systole and often during both phases of the cardiac cycle. Sometimes left-sided pneumothorax occurred; in addition, the air occasionally extended into the subcutaneous tissues of the neck. The roentgenogram often was especially helpful in establishing the diagnosis by the demonstration of air in the mediastinal tissues.

The mechanism of spontaneous mediastinal emphysema has been studied most intensively by Macklin.²² In his experiments on cats he produced interstitial emphysema of the lungs by blowing air through a catheter into a local region of the lung. This caused hyperinflation of the alveoli and leakage of air through numerous ruptures into the spaces about the minute pulmonary vessels. Macklin found that a decreasing pressure gradient developed between the alveoli and the perivascular sheaths so that air continued to pass from the former to the latter. The air then followed the path of least resistance and traveled along the vascular sheaths in blebs of increasing size toward the hilum of the lung; here it ruptured into the mediastinum, collecting in large bubbles and producing the relatively familiar clinical picture. Macklin felt that pulmonary interstitial emphysema was important clinically because these air bubbles encroached upon the space of the pulmonary vascular system, and actually interfered with the circulation through the lung. He was able to demonstrate dilatation of the right heart in cats with interstitial emphysema of the lungs and mediastinum, but the only clinical instance of actual acute right heart failure in this syndrome was reported by Fisher in 1941.²³ His patient was an infant who died three and one-half hours post partum with cyanosis and dyspnea. At autopsy air blebs were demonstrated in the mediastinum and perivascular sheaths of the pulmonary arteries which were compressed and collapsed by the bubbles. The heart showed only dilatation of the right auricle and ventricle. Marcotte and co-workers²⁴ felt that the mechanism of death after intratracheal anesthesia follows exactly the scheme first described by Macklin. H. Miller²⁰ also felt that these air bubbles in the pulmonary sheaths might actually impede the pulmonary circulation with resulting right ventricular embarrassment.

There are no reported fatalities among adults with spontaneous mediastinal emphysema. Quite possibly this is due to general failure to recognize malignant cases and also because this condition is not searched for carefully at autopsy.^{22d} Thus, the demonstration of encroachment upon the pulmonary vascular bed by

air blebs must depend at present upon the clinical and laboratory methods available, the most valuable of these being the roentgenogram and the electrocardiogram. Among the reported cases, no x-ray evidences of dilatation of the right ventricle or enlargement of the pulmonic conus have been noted, although visualization of mediastinal air is not uncommon. The typical electrocardiographic pattern of acute right ventricular strain is characterized by right axis deviation with a prominent S wave in Lead I, a depressed S-T segment in Lead II and often in Lead I, a deep Q wave and an inverted T wave in Lead III, and a diphasic or inverted T wave in Lead IV. The P waves in Leads II, III, and IV also may be large and peaked.^{25,26} These are the classical features of the electrocardiogram of acute cor pulmonale, but all need not be present; a changing tracing is important diagnostically. Although pulmonary embolism most frequently produces this pattern, any process causing rapid interference with the pulmonary arterial circulation may produce a similar electrocardiographic picture. On the basis of Macklin's experiments, spontaneous pulmonary interstitial emphysema may well be one of these factors. Electrocardiograms were reported in the cases of McGuire and Bean,³ Morey and Sosman,⁴ Caldwell,⁸ Griffin,¹⁰ I. Miller,¹¹ Kellogg,¹⁴ Munroe and Webb,¹⁷ Hoffman and co-workers,²⁷ Hamman,²¹ H. Miller,²⁰ and Palatucci and Knighton.¹⁹ In none except the latter few were there any significant abnormalities. Two weeks after the onset of symptoms the patient of Morey and Sosman showed "slight right axis deviation." Caldwell stated that "there are no pathognomonic electrocardiographic changes." Electrocardiographic interpretations were available in three of Hamman's patients: in Case 1 the electrocardiogram was normal. That of Case 4 showed low voltage in Lead I and a diphasic T₂; this patient, however, also had a small left pneumothorax. Another patient (Case 7) was a short, stocky man of 25 years. During an attack the electrocardiogram revealed a prominent S₁ and right axis deviation. No further tracings were made and Hamman did not comment on the significance of this finding in an individual whose physique would suggest that he might normally show left axis deviation. The patient of Palatucci and Knighton revealed general low voltage with no other notable abnormalities. These changes were explained on the basis of the insulating effect of air in anterior pericardial tissues. Three of H. Miller's patients revealed very definite changes of various types, but the patients had pneumothorax, and the distorting effect of this process on the electrocardiogram is well recognized.

In the present case report the classical clinical picture of pneumomediastinum was associated with fever and leucocytosis. With the roentgenogram, it was possible to demonstrate a moderate accumulation of air in the anterior and posterior mediastinum. An interesting point, and one of diagnostic importance, is that with blebs of air surrounding the esophagus in the posterior mediastinum, pain on swallowing became an outstanding symptom. The sounds heard over the precordium were characteristic of those now known as Hamman's sign. Hoffman and associates²⁷ have recently made phonocardiographic records of these sounds in spontaneous emphysema of the mediastinum and have demonstrated that they are synchronous with the cardiac cycle.

The series of electrocardiograms presented in Fig. 3 show the changing pattern in the development of, and recovery from, acute right ventricular strain. It is most likely that this evidence of acute cor pulmonale is a result of encroachment upon the pulmonary arteries by air in the vascular sheaths. Here the electrocardiogram has reproduced what might be expected to occur much more frequently on the basis of Macklin's experimental work. Future cases should be studied from this viewpoint in order to determine whether the mechanism in clinical cases is similar to that of experimental pulmonary interstitial and mediastinal emphysema.

ADDENDUM

Since the completion of this paper, another article has appeared reviewing the syndrome of spontaneous mediastinal emphysema.²⁸

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Abstracts and Reviews

Selected Abstracts

Brummer, P.: The Relation of Neurocirculatory Dystonia to Essential Hypertension, Angina Pectoris, and Peptic Ulcer. *Acta med. Scandinav.* 126:177 (Nos. II-III), 1946.

The author correlated the level of the blood pressure in 1,206 patients manifesting varying degrees of essential hypertension with the previous occurrence of symptoms of neurocirculatory dystonia as determined from careful anamnesis. He found that 26 per cent of those under 40 years of age had had such symptoms for eight years or more in the immediate or remote past. The incidence in patients over 50 years of age was 15 per cent, a difference attributed to the effect of the late war on the younger group in addition to the necessarily less accurate history of older patients. The average incidence for all was 22 per cent.

Fifty per cent of those patients under 40 years who had systolic pressures above 140 mm. Hg. recalled neurocirculatory symptoms, and similarly, 25 per cent of patients who had present or past neurocirculatory dystonia symptoms had systolic blood pressures above 140 millimeters. In patients without evidence of neurocirculatory difficulty the incidence of such hypertension was only 13 per cent. The same relation held for the diastolic pressure levels.

On the other hand, patients over 50 who had significant systolic or diastolic hypertension, had a statistically significant lower incidence of neurocirculatory dystonia, present and past, than those without such grades of blood pressure elevation.

The incidence of neurocirculatory dystonia in 90 patients with peptic ulcer and 66 patients with definite exertional angina pectoris was 16 per cent and 18 per cent, respectively; that is, of the same order as that of the groups as a whole and presumably not greatly different from the incidence in the general population.

The author concludes that the same instability of the vasomotor system that produces neurocirculatory dystonia is, at least in part, responsible for "juvenile hypertension," whereas essential hypertension (at least in those over 50) appears unrelated. He cites the unpublished work of Rahm who examined conscripts of World War I twenty years after their induction examinations and found "in many cases" normal blood pressures in those who had had elevations at the time of the original examination. From this data and his own he suggests the inference that not all hypertension in subjects under 40 years of age is continued in later life. SAYEN.

Weiner, D., and Lange, K.: The Effects and Drawbacks in the Use of Heparin in Retarding Menstruum. *Surgery* 21:102 (Jan.), 1947.

The value of prolonged heparinization is discussed briefly and the literature on retarding menstrua reviewed. Although the clotting times obtained after a single deposition of heparin in Pitkin's menstruum shows considerable irregularity, a satisfactory elevation can be produced for twenty-four hours with large doses in experimental animals.

In small animals, repeated subcutaneous administration of heparin in Pitkin's menstruum leads to the formation of large hematomas which not only trap the heparin and prevent adequate heparinization but frequently cause the death of the animal. These difficulties are overcome in the rat by injection into the tail.

In human beings the small size of hematomas compared to the total blood volume probably renders them less important but great care should be exercised in anemic patients. NAIDE.

Saccomanno, F., Utterback, R. A., and Klemme, R. M.: Anatomic Data Regarding the Surgical Treatment of Angina Pectoris. Ann. Surg. 125:49 (Jan.), 1947.

In dogs from which a length of spinal cord had been removed, stimulation of the isolated spinal nerves was observed to produce cardiac acceleration and a rise in systemic blood pressure when the second to the sixth thoracic spinal nerves were stimulated. No change in heart rate or blood pressure was observed when the eighth cervical or first thoracic spinal nerves were stimulated, indicating that these segments do not convey any cardiac efferent fibers.

The effect on pulse rate was most marked in the second and third thoracic nerves, the effect diminished in the fourth and fifth, and only a very slight effect was observed below the fifth thoracic nerve. The effect on systemic blood pressure was more or less constant from the second thoracic down as far as the seventh thoracic nerve.

These findings suggest a sound anatomic basis for the surgical treatment of angina pectoris. By means of surgical removal or alcohol injection of the second, third, and fourth thoracic sympathetic ganglions on the affected side only, a complete alleviation of anginal pain and a reduction of coronary vasospasm should result. This single surgical procedure does not completely interrupt the pathways of sympathetic effector impulses to the head and upper extremity, since the first thoracic segment which conveys fibers to these areas, but which does not convey cardiac afferent or efferent fibers, remains intact. NAIDE.

Tanna, J. F.: Scalenotomy. An Analysis of Eleven Cases Done for Scalenus Anticus Syndrome. Ann. Surg. 125:80 (Jan.), 1947.

The scalenus anticus syndrome is discussed, and eleven cases presenting symptoms of this entity are reviewed. Seven cases were not associated with a cervical or abnormal rib, indicating that the scalenus anticus syndrome occurs with much greater frequency than the cervical rib syndrome.

The symptoms are the result of spasm of the scalenus anticus muscle, resulting in compression of the brachial plexus and subclavian artery, with the creation of a vicious circle. Attention is called to the fact that many cases of scalenus anticus syndrome may, in reality, be secondary to some other underlying primary pathology.

Scalenotomy may not be necessary in mild cases, since conservative handling is all that is necessary to bring about permanent relief. The results following scalenotomy in the series reported were excellent, only one case of bilateral cervical ribs failed to respond to treatment.

NAIDE.

Miller, H. I., and Miller, P. R.: Refrigeration in Surgery. Am. J. Surg. 72:694 (Nov.), 1946.

The question whether refrigeration prolongs the survival time of anemic tissue remains unanswered. The evidence tends to show that it does. The blessing is not unmixed because of the fibrous replacement of nerve and muscle tissue.

The bacteriostatic action of cold in vivo is on a weak footing. In all the experimental studies cold proved to be of no value. Clinically, it was of value. O'Neil's demonstration of the value of cold in a palmar infection in a patient with scleroderma and in a patient with gas gangrene, and the appearance after refrigeration of gas gangrene in the stumps of two refrigerated limbs, merely outlines the ramifications of the problem.

The published case histories praise the value of cold in shock. Blalock's studies tend to confirm this although his results are not conclusive.

In the elderly toxic patient with gangrene and sepsis, amputation with a tourniquet and refrigeration gives excellent results. Here lies the chief indication for refrigeration amputation. Pain and shock are eliminated and the operation is performed in a bloodless field. NAIDE.

Leitner, St. J.: Electrocardiographic and Spirometric Findings in Boeck's Sarcoid. *Cardiologia* 10:379, 1946.

Myocardial damage is common in Boeck's sarcoid and may be primary or secondary. The latter may result from active lesions or scars, the miliary pulmonary form being less damaging than an extensive sclerotic process. Seventeen patients with this disease were examined. Electrocardiograms were taken at rest, after exercise, after oxygen inhalation, and after gynergen. Oxygen was given to differentiate between organic heart disease and deficient arterialization; gynergen was given to reverse functional electrocardiographic changes. With the patients at rest, there was evidence of myocardial damage in eight patients, probable damage in two, and normal findings in seven. One had congenital heart disease. The electrocardiographic findings were prolonged A-V conduction in five patients, prolonged QRS in two, depressed T waves in five, depressed S-T segments in two, shortened Q-T interval (with hypercalcemia) in four, and supra-ventricular extrasystoles which disappeared after exercise in two patients. After exercise electrocardiographic changes became more abnormal in seven patients, but in one a prolonged P-R interval disappeared. Oxygen inhalation normalized the electrocardiograms of two patients. Gynergen normalized the tracing of one patient and made the tracing of another worse. Of the two patients with evidence of probable damage, the electrocardiogram of one became normal after exercise and one became worse. The authors recognize three possible causes for the electrocardiographic changes: infectious-toxic myocardial damage, right heart strain, and myocardial involvement by the sarcoid. The authors feel that the first is the most common and likely cause.

Spirometric examinations determined the vital capacity, reserve and complemental air, rest minute volume, and respiratory range. In eight patients the spirometric values corresponded with the clinicoradiologic findings. In others the findings did not agree or they showed little change after 3 to 12 months in spite of clinical improvement or deterioration. In general, patients with hilar involvement have better function than those with extensive pulmonary involvement. The results give valuable aid in prognosis. LENEL

Forster, Rudolf: Myocardial Damage in Starvation. *Cardiologia* 10:369, 1946.

Cardiovascular changes were found in all of fifty cases of starvation from German concentration camps. Clinical signs and cardiac failure were rare; changes were found only by electrocardiographic examination. Thirty-one noninfectious patients of all age groups were studied. All had varying grades of edema, cachexia, anemia, hypoproteinemia, and hypocholesterolemia. Fourteen patients showed a relatively low voltage which became higher after therapy. Six had absolute low voltage; two of these patients had tuberculous pericarditis. A relationship of the voltage to the amount and extent of edema was noticed. That edema is not the only mechanism responsible for the low voltage was emphasized by patients with normal voltage in spite of edema or increasing voltage in spite of the persistence of edema. Myocardial damage or hidden pericarditis in the many cases with tuberculosis was thought to be a cause.

Low T waves were found in twenty-nine patients. This change was more conspicuous than low voltage and was found in patients with normal voltage. Inverted or diphasic T waves were found only in patients in whom infectious disease or cardiac disease existed. The S-T segments, and the intraventricular and A-V conduction times were normal. The Q-T interval was prolonged in two moribund patients with diarrhea.

The author concludes that only low voltage and flat T waves are characteristic of inanition and that these changes are both reversible. This was shown by the return of a normal electrocardiogram after therapy.

Clinical examination gave no constant findings: the systolic blood pressure was usually below 100 millimeters, hemic murmurs were absent in spite of anemia, the hearts were normal or small in size, and congestion of the liver was found only on autopsy in a few cases. The edema was not influenced by cardiotonic drugs.

Eighteen patients died of complicating infections. The hearts showed brown atrophy, fatty degeneration, occasionally focal fibrosis, and cloudy swelling.

With regard to the pathogenesis, no constant relation to metabolic changes could be demonstrated. The change of the pH of the blood toward alkalinity is considered important. B₁ avitaminosis, even in the absence of a typical clinical picture, may be a factor. The sum of these changes lead to alterations of the myocardial cellular metabolism which are reversible. They also explain the rapid decline in patients with previous myocardial damage. LENELE.

Merrill, A. J., Morrison, J. L., and Brannon, E. S.: Concentration of Renin in Renal Venous Blood in Patients With Chronic Heart Failure. *Am. J. Med.* 1:468 (Nov.), 1946.

Renal venous blood was obtained through a radiopaque catheter, which had been introduced into an antecubital vein and threaded through the venous system under fluoroscopic guidance into a renal vein. The plasma was separated by centrifugation and, after special preparation, assayed for renin content by injecting it intravenously into anesthetized dogs. Dogs were used because of their relative insensitivity to renin so that a positive result would assure the presence of a significant quantity in the tested material.

Eight of eleven patients with chronic congestive heart failure had significant amounts of renin in their renal venous blood. No renin was demonstrated by this method in arterial blood from these same patients nor in arterial and renal venous blood from five normal subjects.

The authors comment upon the coexistence of the increased concentration of renin in renal venous blood and the vasoconstriction that is present in chronic congestive heart failure. This vasoconstriction maintains arterial pressure despite a reduced cardiac output. Furthermore, renal blood flow is decreased out of proportion to the fall in cardiac output. It is suggested that renin may contribute to these vasoconstrictor phenomena in chronic congestive heart failure.

FRIEDLAND.

Silfverskiöld, B. P.: The Effect of Hemorrhage and Shock on the Caliber of the Abdominal Vena Cava. *Acta physiol. Scandinav.* 12:130 (Nos. 2-3), 1946.

Direct observation of the inferior vena cava in anesthetized rabbits was combined with measurement of pressure through a catheter passed into the lumen by way of the jugular vein. The caliber of the inferior vena cava became smaller when hemorrhage or shock was produced in the rabbits. The average diminution in diameter was from an initial 8 or 9 mm. to 4 or 5 millimeters.

Active constriction of the vein wall and not passive adaptation to a smaller blood content was believed to be the cause of the diminution in size, because (1) the pressure fall within the vena cava was negligible; (2) raising the caval pressure for short periods (thirty seconds) by infusing saline solution into a femoral vein or compressing the liver did not increase the caliber; and (3) tapping the vein with a finger caused a quick return to the original diameter, but the intraluminal pressure was unaltered. Since clamping the carotid arteries in other rabbits was not followed by vena caval constriction the possibility of a carotid sinus reflex as the underlying physiologic mechanism was apparently ruled out.

SAYEN.

Howorth, S., McMichael, J., and Sharpey-Schafer, E. P.: Effects of Venesection in Low Output Heart Failure. *Clin. Sc.* 6:41 (Nos. 1-2), 1946.

The authors studied and compared the effects of venesection and the intravenous administration of 1.5 mg. of digoxin on blood pressure, right auricular pressure, cardiac output, and peripheral resistance in twenty-five patients with "low output" congestive heart failure which was ischemic, valvular, or hypertensive in origin. Both procedures reduced right auricular pressure; venesection transiently, and digoxin often for an "indefinite period." Cardiac output rose significantly whether there was sinus rhythm or auricular fibrillation. In almost all venesected cases the blood pressure fell considerably, and from this fact, a marked decrease in peripheral resistance (site under investigation) was inferred. The blood pressure did not fall, and often rose, after digoxin.

The rise of cardiac output after right auricular pressure was lowered was attributed to the heart's stroke volume lying on the falling, or "overloaded," portion of Starling's ventricular filling curve. Whether digoxin exerted an effect on cardiac contraction in addition to the improved efficiency resulting from lowered auricular pressure could not be determined from the data because the blood pressure fell after venesection. Whereas the heart was doing more work after digoxin, it could not be ascertained if the increased output following venesection would have been maintained under conditions that prevented a decrease of peripheral resistance. SAYEN.

Christensen, B. C.: Variations of the CO₂ Tension in Arterial Blood and the Electrocardiogram in Man. *Acta physiol. Scandinav.* 12:389 (No. 4), 1946.

The author's previous qualitative studies of the effects on the electrocardiogram of hyperventilation, he believes, have proved that the abnormal tracings are not the result of impeded dissociation of oxyhemoglobin, nor of tachycardia; that they occur despite nitroglycerin administration; and that changes in arterial pressure do not accompany them. The calcium ion content does not decrease during hyperventilation tetany, nor does the duration of electrical systole increase, as is sometimes the case in coronary insufficiency. Alteration of intramyocardial pressure with diminished coronary flow due to change in the character of systole and diastole may be the important mechanism involved.

The present study consisted of more quantitative measurements, in two normal subjects aged 30 and 42 years, of alveolar CO₂ tension during the course of hyperventilation experiments. The distinctive electrocardiographic abnormalities, consisting of RST segment depression and T-wave flattening or inversion in two or more leads, began to appear when the alveolar CO₂ tension had fallen from the normal range of 36 to 39 mm. Hg to about 20 millimeters. The changes became greater at pressures of 16 to 17 mm. Hg. They could be abolished or prevented by breathing 2 to 3 per cent CO₂ mixtures.

Since untrained or neurasthenic persons who exercise frequently overventilate, the author thinks that the hypoxemia test is more dependable in the diagnosis of coronary insufficiency than exertion tests. The low oxygen mixture, however, should contain 2 to 3 per cent CO₂ to eliminate the effects of acapnia on the electrocardiogram. SAYEN.

Holmgren, B., and Silfverskiöld, B. P.: The Volume Variations of the Large Central Blood Vessels. *Acta physiol. Scandinav.* 12:134 (Nos. 2-3), 1946.

An important blood reservoir function is ascribed to the heart, aorta, and the great vessels of the thorax. Previous studies are said to have shown that 30 per cent of the blood volume in mice and 26 per cent in rabbits is contained in these structures. The present investigation consisted of thorotrast visualization of these portions of the cardiovascular system of rabbits before and after they were subjected to a severe hemorrhage. After hemorrhage, the heart size and aortic caliber diminished greatly and this appeared to be proportionate to the fall of the systemic blood pressure. Then, somewhat later, the size of the venae cavae decreased without significant internal pressure change. The skin vessel caliber appeared to be unchanged in hemorrhage severe enough to produce the above effects. However, if ether anesthesia was pushed to the point of intoxication in other rabbits, the skin vessels became markedly constricted, whereas little change in the venae cavae was observed.

It is felt that the venae cavae calibers can vary independently of other veins and that this is due to active vasoconstriction rather than passive adaptation to a lower intraluminal pressure, as was apparently the case with the alterations in aortic size. SAYEN.

Massie, E., and Valle, A. R.: Cardiac Arrhythmias Complicating Total Pneumonectomy. *Ann. Int. Med.* 26:231 (Feb.), 1947.

In an analysis of a series of 120 patients undergoing total lung resection, eleven, or 9.1 per cent, were found to have developed a detectable arrhythmia sufficient to endanger the outcome of the operation or at least to cause symptomatic difficulty. The arrhythmias included five instances of auricular fibrillation, four of auricular flutter, and one each of frequent auricular and ventricular

extrasystoles. The right lung was removed in six of the patients developing postoperative arrhythmias and the left in five. The type or location of the lesion had no specific relation to the occurrence of the arrhythmia, although abnormal cardiac rhythms did develop in two of the three patients with involvement of more than one lobe. All the patients developing arrhythmias were 35 years of age or older, the greatest incidence being between the ages of 40 and 70 years. A study of the extent of the anemia before and after the operation and the number of transfusions given the individual patients revealed that these factors had no influence on the development of the cardiac abnormalities. No correlation was detected between febrile reactions and the cardiac disturbances encountered in this study. Medication given prior to the development of the cardiac difficulties also presented no etiological clue.

All the arrhythmias developed within one week after operation, one instance occurred on the second postoperative day, six on the third, two on the fourth, and one each on the sixth and seventh postoperative days. Three of the patients with cardiac arrhythmias died, and an extensive pericarditis was found in two subjects at post-mortem examination.

Twenty-six of the total group of 120 patients presented some evidence of heart involvement prior to operation either on physical or electrocardiographic examination. It is interesting to point out that only in one of these twenty-six cases was a detectable postoperative arrhythmia encountered. The arrhythmias in the remainder appeared in patients with presumably adequately functioning hearts preoperatively. Further study revealed that in addition to the eleven patients who developed abnormal cardiac rhythms, and symptoms therefrom, at least six other individuals showed some objective physical or electrocardiographic evidence of difficulty not present preoperatively.

The authors suggest that the combination of vagal irritation and anoxemia incident to the operation may be responsible for the initiation of the abnormal cardiac rhythms. It is recommended further that the patient's cardiac rhythm must be carefully and frequently observed during at least the first postoperative week in order to determine at the earliest possible moment the onset of abnormal heart action and thus permit early decision as to the therapeutic procedure of choice.

WENDKOS.

Wilhelm, F., Hirsh, H. L., Hussey, H. H., and Dowling, H. F.: The Treatment of Acute Bacterial Endocarditis With Penicillin. Ann. Int. Med. 26:221 (Feb.), 1947.

Eight patients with acute endocarditis were treated with penicillin. In every instance, two or three positive blood cultures had been obtained before treatment was begun. The causative organisms were *Staphylococcus aureus* in two cases, *Staphylococcus albus* in five cases, and a pneumococcus in one case. Five of the patients with staphylococcal infection were heroin addicts who used unsterile syringes for injecting the drug intravenously; and of this number, two were suffering from a complicating malarial infection which had been acquired by the same means.

The initial dose for all eight patients varied between 5,000 and 30,000 units every two to three hours intramuscularly or 200,000 units per day by continuous intramuscular injection. In several patients this dose had to be increased and the largest dose given was 2,000,000 units daily by continuous intramuscular infusion. The duration of treatment did not exceed eight weeks in any instance. Of the eight patients treated, three with staphylococcal endocarditis died before two days of treatment had been completed. A fourth case died because of inadequate dosage. A fifth case died of acute left ventricular failure following severe exertion at a time when the infection had apparently been brought under control by penicillin. Of the three cases who recovered, one had a *Staphylococcus aureus* infection and the other two a *Staphylococcus albus* infection. The case of *Staphylococcus aureus* infection which recovered following the use of penicillin, developed, a year later, another *Staphylococcus aureus* bacteremia. This recurrent infection was unaffected by penicillin, but responded favorably to streptomycin. It is the opinion of the authors that in the five patients who died, treatment was either inadequate or had been started too late.

WENDKOS.

Grollman, A.: Experimental Hypertension in the Dog. *Am. J. Physiol.* 147:647 (Dec.), 1946.

Experimental evidence was obtained in dogs that the hypertension resulting from renal artery constriction has at least two different factors in its pathogenesis. One, which acts immediately, is apparently identical with the generally accepted renal pressor mechanism; it is, however, unrelated to the chronic sustained rise in blood pressure which follows. Even removal of one kidney, the other remaining intact, results in a definite elevation in blood pressure. Removal of a constricted kidney does not abolish chronic hypertension which is maintained for some hours even in the absence of all renal tissue. The bearing of these experiments on hypertension in man is briefly discussed.

KETY.

Page, E. W., Ogden, E., and Anderson, E.: The Influence of Steroids on the Restoration of Hypertension in Hypophysectomized Rats. *Am. J. Physiol.* 147:471 (Nov.), 1946.

Following the establishment of experimental renal hypertension in rats, hypophysectomy or adrenalectomy causes a fall of blood pressure which may in some cases reach levels below normal. The hypertension may then be partially restored by the administration of desoxycorticosterone or adrenal cortical extracts.

KETY.

Richards, O. W., Jr.: Observations on the Dynamics of the Systemic Circulation in Man. *Bull. New York Acad. Med.* 22:630 (Dec.), 1946.

This is a concise review of recent findings by different investigators. The Fick principle and the technique of right heart catheterization are discussed, and the problem of measurement of total peripheral resistance is reviewed. Tables are included showing values for many circulatory functions at rest, during exercise, in hypertension before and after sympathectomy, after administration of a pressor drug, and in various types of shock. The review is well illustrated with pressure tracings from right auricle, right ventricle, aorta, and femoral artery under different conditions.

KETY.

Ensor, C.: The Electrocardiogram of Rats on Vitamin E Deficiency. *Am. J. Physiol.* 147:477 (Nov.), 1946.

The electrocardiogram of rats maintained for one year on a vitamin E deficient diet does not differ from that of normal rats except that a slight widening of the QRS complex occurred infrequently.

KETY.

Rivero Carvallo, J. M.: A New Sign of Tricuspid Insufficiency. *Arch. Inst. cardiol. México* 16:531 (Dec.), 1946.

The author describes a new sign which was demonstrated in 90 per cent of cases with tricuspid insufficiency.

The sign consists of the appearance and intensification of the systolic murmur over the tricuspid area, or the appearance of such a murmur when a murmur was not originally apparent, during deep inspiration or inspiratory apnea. The short inspiratory apnea of crying children may be sufficient to bring out the sign. The sign is attributed to the increased venous return associated with deep inspiration.

LUISADA.

Frau, G.: The Esophageal Lead in the Study of the Auricular Complex. *Folia Cardiol. (Milan)* 5:173 (April 30), 1946.

The author studied the auricular complex by means of a unipolar esophageal electrode. The indifferent electrode was placed on the left leg.

The auricular complex of the normal heart consists of a rapid oscillation (P_{ES}) and a slow terminal wave (T_A).

In most cases of heart disease, the esophageal lead reveals changes of the auricular complex which are not apparent in the classic leads. One case of auricular infarction was revealed by the inverted and cove-shaped T_A . The author advocates systematic use of the esophageal lead in the study of auricular activity.

LUISADA.

Deibert, A. V., and Bruyere, M. C.: **Untreated Syphilis in the Male Negro: III. Evidence of Cardiovascular Abnormalities and Other Forms of Morbidity.** J. Ven. Dis. Inform. 27:301 (Dec.), 1946.

This study is an attempt to follow the natural history of syphilis, uninfluenced by treatment, in adult Negro men, with special reference to its effect on the cardiovascular system. It was found that among untreated syphilitics and presumably unaffected controls, the proportion presenting some evidence of morbid processes of any etiology was considerably higher in the former group: 84 per cent in the syphilitic group and 39 per cent in the unaffected group. The discovered abnormal findings were most frequently associated with the cardiovascular system. The total number of recorded examinations was 423, of which 155 were untreated syphilitics, 115 were infected but had received some treatment, and 153 were believed to be nonsyphilitic. The results of this analysis indicated that the death rate among the syphilitics was more than 75 per cent greater than among the controls, and the life expectancy approximately 20 per cent less. These percentage differences were greatest in the lower age groups.

Dilatation of the ascending portion of the aorta as observed by roentgen study was shown to be more frequent in syphilitics of all ages than in controls. Definite abnormality of the aorta was observed in about 40 per cent of the syphilitics above the age of 65, while it was present in only 10 per cent of the controls. The heart size, as determined by the ratio of the transverse diameter of the heart to the internal diameter of the thorax, indicated more abnormality in the syphilitic group. The systolic and diastolic blood pressures, as well as the pulse pressures, were higher in syphilitics than in nonsyphilitics. Examination of the radial, brachial, and temporal vessels revealed evidence of arteriosclerosis more frequently in the syphilitic than in the control group. In the younger age group, the percentage of the syphilitics in whom evidences of arteriosclerosis could be detected was significantly greater than in the controls.

BELLET.

Moritz, A. R., and Zamecheek, Norman: **Sudden and Unexpected Deaths of Young Soldiers.** Arch. Path. 42:459 (Nov.), 1946.

The authors, in reviewing more than 40,000 autopsy protocols received at the Army Institute of Pathology between January 1942 and January 1946, collected approximately 1,000 cases of sudden death from disease in apparently healthy soldiers under the age of 40 years. An examination of between 700 and 800 of the protocols shows that three principal categories included the majority of these cases.

Organic heart disease accounted for approximately 250 of these unexpected deaths. Of this number, more than 200 were due to coronary arteriosclerosis, and 34 to other forms of cardiac disease. Of the coronary cases, 115 were selected for statistical study. With increasing age there was rapid rise in incidence, even in this group composed of young men. Negroes were definitely less susceptible than white persons to sudden "coronary" death. The authors did not find obesity to be a significant factor. Their data, in reference to the degree of exertion associated with sudden death from coronary disease, "do not prove or disprove a cause and effect relationship between physical activity and acute heart failure." Their analysis of ninety-eight coronary cases showed that thirty-three died in sleep, seventeen died during "strenuous exercise," and the remainder died while in a state of inactivity, or during the course of ordinary activity. The authors concur in the general opinion that violent exercise is probably dangerous for persons suffering from severe coronary disease. In all instances, severe atherosclerosis in one or both coronary arteries was disclosed by post mortem examination. Complete occlusion was absent in 55 per cent of the group, and bleeding into an atheromatous plaque was infrequent. In the large majority of cases the heart was within normal weight limits.

In the group of thirty-four cases of sudden death from cardiac disease other than coronary arteriosclerosis, there were fourteen instances of "idiopathic" acute myocarditis, five of extensive diffuse (chronic) myocarditis, six cases of syphilitic aortitis, and five cases of rheumatic heart disease.

The second great category was nontraumatic intracranial hemorrhage. This group consisted of ninety-one cases of which sixty-nine died of subarachnoid hemorrhage from congenital "berry" or "miliary" aneurysms. In this group whites predominated heavily over Negroes. Body weight seemed to be of little or no significance. There was no instance of direct cranial trauma, but strenuous physical activity was an important predisposing factor. This group of cases was arbitrarily limited to cases that did not survive more than twenty-four hours. In the majority of cases the fatal seizure was preceded by headache and vomiting, and in many cases by fecal and urinary incontinence. In this group of sixty-nine cases there were three in which there was clinical proof of blood leakage before the fatal rupture; lumbar puncture disclosed bloody spinal fluid twelve days, two months, and six months before the occurrence of the fatal hemorrhage. When these soldiers had their fatal attack they were thought to have made a complete recovery from their previous involvement.

In sixteen other cases, although spinal fluid examination was not done, there was clinical evidence of cerebral disturbance which was present from a few days to many months before the fatal attack. Severe headaches, nausea, attacks of stiff neck, malaise, and evanescent nerve palsies were noted in this group. Necropsy later revealed that the latter sign was the result of an adherent aneurysm with burrowing hemorrhage. It was apparent that when blood was extravasated into the adjacent brain substance through rupture of a superficial aneurysm it was less likely to be fatal than when blood escaped directly into the subarachnoid space. The burrowing hemorrhage therefore was considered evidence of previous involvement, and of organic fixation of the aneurysm to the adjacent brain surface.

In eighteen of the ninety-one cases of unexpected death due to intracranial hemorrhage, the origin of the bleeding was an intracerebral vessel, in contrast to the subarachnoid location of the congenital aneurysms. In five of these "internal brain hemorrhages" an aneurysm was the cause, the aneurysm in all five cases occurring in one or another branch of the middle cerebral artery. In every instance the hemorrhage had ruptured into a lateral ventricle. There were four cases of primary subarachnoid hemorrhage due to a lesion other than congenital aneurysm, namely angioma. It is interesting that there were thirteen instances of intracerebral bleeding in which neither the exact site or nature of the vascular defect could be recognized. In all of these cases the hemorrhage originated in the lenticulostriate region. The soldiers who developed this condition were never previously ill and necropsy did not reveal any evidence, other than the hemorrhage, of cerebral vascular disease.

The third great category is comprised of sudden deaths due to meningococcic infections. A complete analysis of the extensive data in connection with this category probably does not fall within the province of this review. It is interesting, however, that in this very large group made up entirely of young adults, all of the symptomatology and physical signs included in the Waterhouse-Friderichsen syndrome, previously noted almost exclusively in children, were present in their fullest development. No effort was made to appraise the severity or functional significance of the myocardial involvement; the authors mention instances of focal, diffuse, and occasionally dense polymorphonuclear and monocytic infiltration of the myocardium.

The fourth category is composed of 140 carefully investigated cases in which postmortem findings were negative. Very small or questionable coronary artery lesions were considered as negative findings. The majority of the soldiers showed only "agonal" changes, indicative of acute circulatory failure (acute systemic anoxia). It is entirely possible that unexplained poisoning may have been a factor in some cases, but circulatory death in most of them was apparently indisputable.

GOULEY.

Littman, D.: Electrocardiographic Phenomena Associated With Spontaneous Pneumothorax and Mediastinal Emphysema. *Am. J. M. Sc.* 212:682 (Dec.), 1946.

Two cases of mediastinal emphysema with spontaneous left-sided pneumothorax are described, and the electrocardiographic changes analyzed, together with those of similar cases reported in the literature. It is evident from these studies that gross electrocardiographic changes in the presence of mediastinal emphysema and left-sided pneumothorax are observed only in the CF leads, and can be obtained only when the patient is in the supine position. When the patient is in the prone, erect, or right lateral position the tracings are essentially normal. The CR leads are normal in any position, although the height of the T waves and size of the QRS excursions show variations. For these changes to occur it is necessary that the patient have both mediastinal emphysema and left-sided pneumothorax and the pneumothorax must be present in front of the heart. Thus the changes noted are not the result of interference with coronary filling as has been postulated by some, but rather, result from the presence of air between the heart and the exploring electrode, causing interference with electrical conduction. It is recommended that CF leads be made in various positions in the presence of spontaneous pneumothorax and mediastinal emphysema.

DURANT.

Stewart, H. J., Newman, A. A., and Evans, W. F.: Levels of Blood Pressure in Both Arms and Legs in Normal Subjects and Patients Suffering From Certain Disease. *Am. J. Med.* 1:451 (Nov.), 1946.

The authors confirm the observation made by other investigators; namely, that in normal subjects the systolic, diastolic, and pulse pressures are higher in the legs than in the arms. The pulse pressure in the legs is widened by a greater rise in systolic than in diastolic pressure.

In normal subjects the average systolic pressures in the legs exceeded that in the arms by 33.6 mm. Hg and the diastolic pressures in the legs exceeded the arm pressure by 25.1 millimeters. In thirteen patients with rheumatic mitral valve lesions, the average systolic and diastolic arm and leg pressures did not deviate significantly from those in normal subjects. In eleven patients with congenital heart disease the average systolic and diastolic arm pressures were not significantly different from those of normal subjects but the average systolic and diastolic leg pressures were only 11 to 13 mm. Hg higher than the pressures in the arms. Ten patients with Graves' disease averaged slightly higher systolic and diastolic pressures both in the arms and legs as compared with the normal subjects. Fifteen hypertensives had systolic leg pressures which averaged 43.5 mm. Hg higher than the pressure in the arms but the diastolic pressure averaged only 29 mm. Hg higher than the arm pressures. In eleven patients with rheumatic aortic insufficiency and mitral stenosis and insufficiency, the average systolic and diastolic pressures in the legs were higher than in the arms and the average pulse pressure differences in the legs were greater than in normal subjects and in patients with mitral valvular lesions alone.

The most significant differences were observed in patients with coarctation of the aorta. Of twenty-three patients, twenty-two exhibited systolic and diastolic pressures which were lower in the legs than in the arms. The authors emphasize the necessity for estimating the blood pressure in the legs of all patients with hypertension if patients with coarctation of the aorta are not to be overlooked.

FRIEDLAND.

Jervell, O.: Paroxysmal Tachycardia, Transitory Flutter and Fibrillation. *Acta med. Scandinav.* 125:295 (4), 1946.

Among 7,000 subjects studied electrocardiographically, from 1941 to 1944, there were 168 with paroxysmal arrhythmias. These included nine with "paroxysmal sinus tachycardia" (focus believed to be in the lower portion of the S.A. node), three with paroxysmal nodal rhythm, and one with paroxysmal ventricular tachycardia. The remainder had paroxysmal auricular flutter, fibrillation, or paroxysmal auricular tachycardia.

Seventy patients (thirty-three with fibrillation) had no evidence of organic heart disease or thyrotoxicosis. In many of these such possible predisposing factors as adiposity, infectious processes, recent exhausting exertion, chest deformity, pregnancy, and "digestive reflex neurosis"

were thought to be significant. Degenerative heart disease was diagnosed in sixty-seven, rheumatic heart disease in sixteen, and thyrotoxicosis in eleven of the patients with organically diseased hearts. The author believes that both a predisposing and a precipitating cause can be found in most instances of paroxysmal arrhythmia, the former being some organic or functional alteration of the auricular myocardium, and the latter a derangement of the autonomic nervous system, usually an increased sympathetic tone. SAYEN.

David, A. R., and Lipsitch, L. S.: Clinical Aspects of Calcification of the Mitral Annulus Fibrosus. Arch. Int. Med. 78:5 (Nov.), 1946.

The authors discuss the clinical aspects of calcification of the mitral annulus fibrosus and describe the physical signs and electrocardiographic changes that occurred during the life of ten such patients (ages 58 to 82 years). They point out that the lesion has been of incidental interest to the roentgenologist and pathologist. There was no evidence that the lesions in any of the cases presented were on a rheumatic basis; the etiologic factor seemed to be arteriosclerosis, which was invariably a marked finding.

The clinical findings revealed two cases of angina pectoris and five cases of congestive failure. Half of the patients reported showed complete heart block. It was interesting to note that seven of the ten patients had loud, rough systolic murmurs, and that four of the ten had blowing, apical diastolic murmurs (thought to be related to auricular activity). There was a definite correlation between the diastolic murmurs and the heart block. None of the murmurs were thought to be associated with either mitral stenosis or regurgitation.

It is believed that heart block may be expected when the calcification spreads into the septum, particularly when excrescences reach out from the ring to invade the conducting system more deeply.

The authors ventured to diagnose mitral annulus fibrosus on the basis of complete heart block, and apical diastolic murmur in elderly patients without a history of rheumatic fever. The diagnosis was confirmed by x-ray in three of the reported cases. HORWITZ.

Manlove, F. R.: Retinal and Choroidal Arterioles in Malignant Hypertension: A Clinical and Pathologic Study of Fifteen Cases. Arch. Int. Med. 78:4 (Oct.), 1946.

Manlove reviewed the literature on retinal and choroidal arteriolar changes in malignant hypertension, then discussed the clinical and pathologic changes found in fifteen patients between the age of 20 and 70 years (60 per cent of these patients were 50 years of age or over). In order of frequency, the symptoms were as follows: cardiac, central nervous system, general, visual, renal, and gastrointestinal. Of the fifteen patients, fourteen had albuminuria, four had casts in the urine, over half had a secondary anemia, and all had retention of urea and creatinine.

At autopsy, cardiac hypertrophy was an invariable finding, and in nearly every patient the kidneys were small and exhibited pitting and scarring of the surfaces. Sections of the eyes, cut to include the nerve head and macular area, were studied in the fifteen patients, as well as in seven controls. The vascular lesions included: 1. subendothelial proliferation of the arterioles of the choroid, but rarely of the retina; 2. medial thickening; 3. a perivascular fibrous tissue increase; 4. a varying degree of hyaline degeneration in the choroidal arterioles; and 5. occasional acute necrosis of the choroidal arterioles or infiltration of fat into the arteriolar wall.

There was also noted a marked reduction of the lumen-to-wall ratio in malignant hypertension, as compared to the controls. It is interesting to note that the percentage reduction from the normal mean was greater in the choroid and retina than in any other organ except the kidney. HORWITZ.

Rosenblueth, A., and Ramos, J. G.: The Various Components of the Monophasic Electrocardiogram of the Ventricle. Arch. Inst. cardiol. México 16:45 (Mar. 31), 1946.

The normal monophasic electrocardiograms of the ventricle of different animals (frog, turtle, cat, and dog) are similar and complex. They present several deviations or oscillations in the course of the main wave. These are modified independently by various experimental procedures. The assertion that the various oscillations are due to artefacts is refuted.

An evaluation of the factors which may produce the alternations of response leads to the conclusion that alternation of the electric phenomena may occur in a given group of active fibers and may even take place in a single fiber.

LUISADA.

Pallares, D. S., Paras, O., Cosio, E. C., and Mendoza, F.: The Intrinsic Deflection in Normal Cases and in Ventricular Hypertrophy. Arch. Inst. cardiol. México 16:397 (Oct. 31), 1946.

A study of the intrinsic deflection was made in 100 healthy persons. In every case the onset of the intrinsic deflection was earlier in leads taken from the right side than in leads from the left side of the precordium.

In only two normal cases, the intrinsic deflection was inscribed after 0.03 second in V_1 or V_2 ; in fourteen normal cases, the value of 0.045 second was exceeded in V_5 or V_6 .

The fact that in some normal persons the QRS complex is M-shaped in leads made with the chest electrode on the right side of the precordium and causes a delay in the onset of the intrinsic deflection shows the importance of caution in interpreting the value of the intrinsic deflection in V_1 or V_2 , where no other electrocardiographic abnormalities are noted.

One hundred tracings in which an onset of the intrinsic deflection in V_1 or V_2 occurred more than 0.03 sec. after the beginning of the ventricular complex were chosen at random. (Normal electrocardiograms and tracings showing right bundle branch block were excluded.) Rheumatic heart disease with mitral involvement was present in 91 per cent of the cases; chronic cor pulmonale was present in 5 per cent; tetralogy of Fallot in one per cent; congenital pulmonary stenosis in one per cent; luetic aortitis in one per cent; and arterial hypertension in one per cent. The patient with luetic aortitis showed pulmonary emphysema and dilatation of the right ventricle at autopsy. In every patient, except the patient with arterial hypertension, right ventricular hypertrophy was demonstrated by x-ray.

One hundred cases with an onset of the intrinsic deflection in V_5 or V_6 0.04 to 0.045 sec. after the beginning of the ventricular complex were studied. In 96 per cent of the cases some heart disease with hypertrophy of the left ventricle, shown by clinical or x-ray examination, was present. There were persons with normal hearts in this group.

One hundred cases with an onset of the intrinsic deflection in V_5 or V_6 0.045 to 0.05 sec. after the beginning of the QRS complex were studied. In 97 per cent, heart disease with left ventricular hypertrophy was present. Three persons with normal hearts were found in this group.

One hundred cases with the onset of the intrinsic deflection in V_5 or V_6 0.05 to 0.055 sec. after the beginning of the QRS complex were studied; 98 per cent showed evidence of heart disease and left ventricular hypertrophy. Fifty cases had rheumatic heart disease with aortic insufficiency. This finding is of help in proving or eliminating aortic insufficiency where there is a basal diastolic murmur without an accompanying high pulse pressure.

Twelve cases with a late intrinsic deflection in leads recorded from the right as well as the left side of the precordium were studied. All had advanced myocardial disease with diffuse ventricular enlargement.

Fifty cases with considerable left ventricular enlargement were studied. The intervals between the beginning of the QRS and the intrinsic deflection in V_5 or V_6 were as follows: 5 cases, 0.03 to 0.04 sec.; 18 cases, 0.04 to 0.05 sec.; 20 cases, 0.05 to 0.06 sec.; 5 cases, 0.06 to 0.07 sec.; one case above 0.07 sec., and one case in which the intrinsic deflection could not be determined. The comparison of these figures with the figures found in 100 normal cases strongly supports the view that the delay in the onset of the intrinsic deflection is produced by left ventricular hypertrophy.

In fifty cases with an x-ray showing right ventricular hypertrophy the interval between the beginning of the QRS complex and the onset of the intrinsic deflection in V_1 or V_2 was as follows: two cases, 0.01 to 0.02 sec.; 15 cases, 0.02 to 0.03 sec.; 14 cases, 0.03 to 0.04 sec.; 7 cases, 0.04 to 0.05 sec.; 3 cases, 0.07 to 0.08 sec.; and one case, 0.08 second. It is pointed out that in 60 per cent of these cases the onset of the intrinsic deflection occurs more than 0.03 sec. after the

beginning of the ventricular complex. These results are not so uniform as those that apply to the left ventricle, but they show deviations when compared with the results obtained in normal cases.

The study of the intrinsic deflection in the precordial leads has great value in the diagnosis of left ventricular hypertrophy.

AUTHORS.

Klinefelter, E. W.: Significance of Calcification for Roentgen Diagnosis of Aneurysm of the Abdominal Aorta. Radiology 47:597 (Dec.), 1946.

The roentgen diagnosis of aneurysm of the abdominal aorta has been made in only 20 per cent of more than 1,000 cases recorded in the literature. The author presents three proven cases and discusses the diagnostic roentgen findings. The patients were all men, over 65 years of age, and suffered from chronic hypertension and far-advanced arteriosclerosis. The serology was negative in all three patients. One patient sustained a rupture of the aneurysm which, by the seepage of the blood retroperitoneally in the region of the rectum, produced filling defect of the rectum. This defect was demonstrated by barium enema. His chief complaint, over a period of six months, was pain in the right lower abdominal quadrant. The ruptured aneurysm was revealed when an operation was performed for suspected appendicitis. The other two patients presented no complaints directly referable to their aneurysms; one died of uremia secondary to prostatic carcinoma, the other died of coronary occlusion.

The diagnostic roentgen criteria, described in the literature, for aneurysm of the abdominal aorta are (1) vertebral erosion, (2) presence of a soft-tissue mass, (3) organ displacement, and (4) calcification. The author calls specific attention to the importance of differentiation between the calcification seen in the wall of the arteriosclerotic abdominal aorta and calcification in the wall of the aneurysm. In the former instance, the calcification tends to outline the length and width of the aorta through the major part of its course, while in the latter only a portion of the aneurysmal wall is outlined on the film by either a single, curved, continuous line or by a broken line of calcification; a considerable portion of the wall is ill-defined and requires careful study of the film to detect the indistinct calcification.

MERANZE.

Leys, D.: Rheumatic Encephalopathy. Edinburgh M. J. 53:444 (August), 1946.

This author reports the presence in three girls, all at or past puberty, of acute rheumatic fever and chorea, associated with an unusual type of psychosis. Two of these patients were seen by a consulting psychiatrist, who diagnosed them as schizophrenic. All recovered sufficiently to resume active life and were in good health one year after the illness.

This author suggests that the three girls suffered from rheumatic encephalitis because puberty coincided with a period not only of prevalence of rheumatic fever but also with prevalence or enhancement of pathogenic neurotropic virus. Rheumatic psychosis of various types, including schizophrenia, has been described by neurologists or psychiatrists in studies of psychosis or encephalitis, but it does not seem to have been remarked by pediatricians. Chorea, or rheumatic encephalopathy, would appear to be very much modified by the age, sex, constitution, and experience of the victim, and very possibly by endocrine or biochemical factors.

BELLET.

Govan, Clifton D., Jr.: The Effect of Salicylate Administration on the Prothrombin Time. J. Pediat. 29:629 (Nov.), 1946.

The author investigated the effect of varying doses of salicylates upon the prothrombin time in twenty-four children. Most of the patients were entirely well, three had acute rheumatic fever, and three suffered from acute hemorrhagic nephritis. Eighteen showed no significant change in prothrombin time, while six had abnormal prolongation. The most marked hypoprothrombinemia occurred between the second and the fifth day and in each of the six patients normal pretreatment levels were reached by the ninth day despite continuous salicylate administration. The prothrombin deficiency attending the therapeutic administration of salicylate is neither a constant nor a dangerous feature. The mechanism of hypoprothrombinemia production by salicylate is unknown; however it is most probably the result of changes in the liver effected by salicylate.

HAUB.

Jackson, Robert L.: Heart Disease in Children in a Rural Town County; Particularly in Relation to Rheumatic Fever. *J. Pediat.* 29:647 (Nov.), 1946.

The calculated incidence of active rheumatic fever in the school population of Washington County, Iowa, was 0.61 per cent. The total incidence of organic heart disease was 0.47 per cent. The etiology of the organic disease was rheumatic in 58 per cent; the etiology in the remainder was congenital disease. These results were obtained as a by-product of a planned diagnostic survey conducted over the period of 1940 to 1945. HAUB.

Faber, M.: The Cholesterol Content of the Human Aorta in Relation to the Serum Cholesterol Concentration. *Acta med. Scandinav.* 125:418, 1946.

The cholesterol content of a section of unit size, taken from the media and intima of the ascending aorta, was compared with the serum cholesterol content and correlated with age in normal persons (victims of death by accidental shooting), in hypertensive patients and, in patients with xanthomatosis. It was found that in normal persons the aortic cholesterol content rose slowly with advancing age but showed no parallel with the serum content. In essential hypertension the aortic cholesterol increased at a more rapid rate than in normal individuals but the serum content did not; whereas the xanthomatosis cases studied showed a rise in both aortic and serum cholesterol. SAYEN.

Kjergaard, H.: Patent Ductus Botalli in Three Sisters. *Acta Med. Scandinav.* 125:339, 1946.

The author reports three cases of patent ductus arteriosus in a family that included five children. He suggests that the rarity of reports of similar occurrences in the literature may be due to failure to examine thoroughly all members of families in which a case of congenital heart disease has been discovered. SAYEN.

van Buehem, F. S. P.: Extensive Calcification in the Heart at an Early Age. *Acta med. Scandinav.* 125:182, (d) 1946.

A girl, 18 years of age, with a three-year history of many painless collapses after overexertion, excitement, or passage from a cold to a warm environment, developed exertional interscapular pain with bilateral arm radiation to the arms and, finally, congestive heart failure, from which she died. Her blood pressure was 135-90. Cyanosis of hands and feet was present. The Electrocardiogram showed right axis deviation and RS-T segment depression in Leads II, III, and IVF. Serum calcium was 13.2 mg. per 100 ml. and serum cholesterol, 223.

Necropsy showed marked right ventricular hypertrophy and extensive calcification in the endocardial and subendocardial musculature of the left ventricle. The coronary arteries were normal. No conclusive explanation for the calcification could be found but it was proposed that the left ventricular endocardium had been injured by previous exertion and that calcium had been deposited at the sites. SAYEN.

Frost, J.: A Comparison Between the Leads from the Extremities, the Precordial Leads CF₂ and IVF, and Nehb's Leads, With Special Regard to the Diagnosis of Infarction. *Acta med. Scandinav.* 125:15, 1946.

In a study of 221 persons, 110 with heart disease, including 25 with myocardial infarction (eight autopsies), comparisons were made of the relative value of limb leads, chest leads (CF₂ and IVF) and Nehb leads. The latter were taken from the angles of a triangle formed by points in the second left intercostal space anteriorly near the sternum, the cardiac apex, and the projection of the apex in the posterior axillary line. It was found in rare cases that Nehb's "D" Lead (exploring electrode posteriorly, indifferent electrode in the second left intercostal space) showed an abnormal pattern when Leads II and III did not, and might, therefore, be used as a

supplement to the standard leads in the diagnosis of posterior infarction. Usually Nehb's leads revealed no abnormalities that were not revealed also in the limb leads, CF₂ and IVF. The importance of serial tracings and the value of taking Leads CF₃ and CF₅ in addition to the Nehb and other leads are stressed.

SAYEN.

Gilbert, R. A., and Goldzieher, J. W.: The Mechanism and Prevention of Cardiovascular Changes Due to Insulin. *Ann. Int. Med.* 25:928 (Dec.), 1946.

Following the administration on different days of insulin alone, of insulin with prostigmin, and of adrenalin alone, the authors studied the effects on the cardiovascular systems of three healthy young adults and of five patients over 50 years of age with diminished cardiac reserve. They employed insulin with adequate amounts of glucose to prevent any lowering of the blood sugar in 10 other subjects used as controls. Their results indicated that either insulin (only when hypoglycemia is allowed to develop) or adrenalin will augment the heart rate and blood pressure in all subjects and, in those with an already lowered cardiac reserve, will also elevate the venous pressure and reduce blood velocity. They also observed that these effects induced by insulin hypoglycemia are prevented by the supplemental administration of prostigmin. Finally, it was observed that analagous changes in the ST segment and T waves of the electrocardiogram occurred in those with diminished cardiac reserve following the administration of either insulin or adrenalin alone. This latter phenomenon is interpreted by the authors to signify that electrocardiographic changes evoked by insulin are to be related to heightened sympathetic activity reflexly induced by the hypoglycemia.

WENDKOS.

de la Barreda, P., and de Molina, A. F.: Conclusions Based Upon Experiments With Hypertension in a Dog, Hypertension in a Cow, and Pepsin. *Rev. clin. españ.* 23:114 (Oct. 31), 1946.

Renin, obtained from the plasma of a dog free from hypertensinase, does not raise the blood pressure in a normal anesthetized dog, when injected with hypertensinogen of a cow. Inconclusive results are obtained when the plasma is incubated with dog's hypertensinogen.

Renin extracts obtained from calf kidney cortex and incubated with dog's hypertensinogen did not produce hypertension. The same calf's renin when incubated with cow's hypertensinogen always produced a hypertensive effect.

Dog's renin incubated with dog's hypertensinogen produced hypertension.

The extracts obtained by incubation of pepsin with cow's hypertensinogen produced variable effects. The same extracts incubated with dog's hypertensinogen were ineffective.

It was concluded, therefore, that a specificity of the renin-hypertensinogen reaction does exist. In studying the comparative changes of the plasma hypertensinogen, the need to use renin obtained from kidneys of the same animal species is pointed out.

AUTHORS.

Salazar Mallén, M., and Madel Refugio Balcàzar, Q. B. P.: Influence of Sodium Salicylate on the Antigen-Antibody Reaction. *Arch. Inst. cardiol. México* 16:432 (Oct. 31), 1946.

The author studied the action of sodium salicylate, both in an albumin-antialbumin and in a streptolysin-antistreptolysin system. The specific precipitates are inhibited in vitro by sodium salicylate. This action is specific because a similar effect is not obtained with antipyrine.

Sodium salicylate seems to combine with the antistreptolysin, thereby interfering with the possible neutralization of streptolysin.

LUISADA.

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